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ABOUT COVER

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AIMS AND SCOPE

The primary aim of World Journal of Clinical Cases (WJCC, World J Clin Cases) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The WJCC is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJCC as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The WJCC’s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ying-Yi Yuan; Production Department Director: Xu Guo; Editorial Office Director: Jin-Lei Wang.
Evolution of *World Journal of Clinical Cases* over the past 5 years

Sathish Muthu

**Abstract**

Analysis of the articles published in any journal is necessary to ascertain the performance of the journal in the academia. The author made a scientometric analysis of the articles published in the *World Journal of Clinical Cases* in the past 5 years and present the data to the readers.

**Key Words:** *World Journal of Clinical Cases*; Scientific journal; Research publication; Keywords; Scientometrics; Trend analysis

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**Core Tip:** We analysed the articles published in the *World Journal of Clinical Cases* to illustrate the journal performance in the past 5 years. The author demonstrated that the journal has been growing with time with appropriate publication standards as per theCOPE guidelines. The journal has a wide spectrum of published articles covering various domains of medicine to meet the aims and scope of the journal.

**Citation:** Muthu S. Evolution of *World Journal of Clinical Cases* over the past 5 years. *World J Clin Cases* 2022; 10(24): 8432-8435

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i24/8432.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i24.8432
INTRODUCTION

The World Journal of Clinical Cases started out publishing high-quality peer-reviewed articles since 2013 [1]. In this letter I would like to present a short summary of the performance of the journal in the past 5 years. A scientometric analysis was performed using the metadata of the articles published in the journal and indexed in Web of Science and Reference Citation Analysis [2] database over the past 5 years (2017-2021). Visualisation of the data was made using CiteSpace software [3].

Publication volume

The journal published 2792 articles between 2017 and 2021. The journal experienced three times growth in the number of publications with 12 issues in 2017 covering 452 pages in Volume 5 to 36 issues in 2021 covering 11508 pages in Volume 9. Similarly, the number of published articles rose from 71 in 2017 to 1296 in 2021 as shown in Figure 1.

Institutional network

Of the 2792 analysed articles, the top contributors were from Zhejiang University (143), Capital Medical University (129), China Medical University (99), Sichuan University (91), and Jilin University (82).

Country network

The People’s Republic of China contributed to 71% (1982) of the total publications in the past 5 years, followed by South Korea (160), United States (127), Japan (111), and Italy (74).

Cited references

In order to analyse the self-citation policy, analysis was made on the journals of the cited references from the included publications in the past 5 years. A total of 731 journals were cited in the 31774 references analysed. The top cited journals were New England Journal of Medicine (622), Lancet (538), World Journal of Gastroenterology (518), Medicine (460), and PLOS One (416). This proves that the journal was adherent to the self-citation policy with only 122 self-citations, which account for 0.3% of the total references analysed.

Keyword cluster analysis

On analysing the keywords of the included articles, clustering of the keywords was made to represent the subject of the included articles. The top clusters in the included articles were #0 case report, #1 colorectal cancer, #2 inflammatory bowel disease, #3 hepatocellular carcinoma, #4 neoadjuvant chemoradiotherapy, and #5 coronavirus disease. Network of the included clusters is represented in Figure 2.

Publication trend analysis

On analysing the timeline of the keywords among the top clusters we noted that the recent publication trends revolved around the research domains like oncology, chemoradiotherapy, and coronavirus disease as shown in Figure 3.
Citation Analysis

The 2792 articles published in past 5 years accumulated a total citation count of 5285 (as of June 6, 2022). Average citation per article was 1.89. Based on the articles published in the past 5 years, the H-index of the journal was 22 (as of June 6, 2022). The article by Ren et al.[4] titled “Fear can be more harmful than the severe acute respiratory syndrome coronavirus 2 in controlling the coronavirus disease 2019 epidemic” is the most cited article of the journal with 134 citations (as of June 6, 2022). The rate of publication and the citation frequency are given in Figure 4. The journal demonstrates a Journal Impact Factor of 1.534 based on Journal Citation Reports 2022 and Journal Article Influence Index of 1.89[2] ranking 135 among 172 journals in the category of Medicine, General and Internal[5].

CONCLUSION

We demonstrated that the journal has been growing with time with appropriate publication standards as per the COPE guidelines[6]. The journal has a wide spectrum of published articles covering various
Figure 4 Relationship between annual publications and citations.

domains of medicine to meet the aims and scope of the journal.

FOOTNOTES

Author contributions: Muthu S contributed to conceptualization, methodology, formal analysis and investigation, original draft preparation, manuscript review and editing, resources, and supervision.

Conflict-of-interest statement: The author is an editorial board member of the World Journal of Clinical Cases.

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Country/Territory of origin: India

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S-Editor: Liu JH
L-Editor: Wang TQ
P-Editor: Liu JH

REFERENCES
2 Reference Citation Analysis - Baishideng Publishing Group. Available from: https://www.referencecitationanalysis.com/
3 Chen C. CiteSpace: A Practical Guide for Mapping Scientific Literature
4 Ren SY, Gao RD, Chen YL. Fear can be more harmful than the severe acute respiratory syndrome coronavirus 2 in controlling the corona virus disease 2019 epidemic. World J Clin Cases 2020; 8: 652-657 [PMID: 32149049 DOI: 10.12998/wjcc.v8.i4.652]
NF-κB: A novel therapeutic pathway for gastroesophageal reflux disease?

Mao-Lin Zhang, Long-Qing Ran, Meng-Jun Wu, Qin-Chen Jia, Zhi-Ming Qin, Yong G Peng

Abstract

Although gastroesophageal reflux disease (GERD), a common chronic disease in clinical practice, has been widely studied, its potential adverse impact on patients is still a significant clinical concern. It is necessary to understand the pathogenesis of the disease and choose appropriate treatment according to its mechanism. The pathogenesis of GERD is diverse and complex. As the traditional treatment methods are expensive and ineffective in alleviating symptoms in some patients, new treatment options need to be explored. Our previous study suggested that the activation of nuclear factor-kappa beta (NF-κB) in esophageal mucosa may be related to the injury of epithelial barrier function caused by reflux. Based on the literature and our previous study results, it is speculated that inhibition of NF-κB activation may block the insult of GERD on the esophageal mucosal barrier. NF-κB may play an important role in the development of GERD. This article reviews the pathogenesis of GERD and the relationship between NF-κB and GERD, in order to provide new strategies for the treatment of GERD.

Key Words: Gastroesophageal reflux disease; NF-κB; Pathogenesis; Mechanism; Inflammatory injury; Esophageal epithelial barrier
**Core Tip:** Gastroesophageal reflux disease (GERD) is one of the most common chronic diseases. Current treatments, including drugs and surgery, have significant side effects and some patients do not respond to treatment. This article reviews the pathogenesis of GERD, especially the relationship between the NF-κB pathway and GERD. We also assessed the latest studies on the effects of drugs inhibiting the NF-κB pathway in GERD, providing new possibilities for the treatment of GERD.

**Citation:** Zhang ML, Ran LQ, Wu MJ, Jia QC, Qin ZM, Peng YG. NF-κB: A novel therapeutic pathway for gastroesophageal reflux disease? World J Clin Cases 2022; 10(24): 8436-8442
**URL:** https://www.wjgnet.com/2307-8960/full/v10/i24/8436.htm
**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i24.8436

**INTRODUCTION**

Gastroesophageal reflux disease (GERD) is a common clinical disorder in western countries[1]. Symptomatic GERD affects 10%-20% of the population in the western world and 5% of the population in Asia including China. GERD is a serious complication in patients who undergo esophagectomy and gastric tube reconstruction due to cancer. Approximately 50% of patients with esophageal cancer have GERD symptoms after surgery, including burning sensations in the pharynx and neck, obstruction when eating, cervical heartburn, belching, acid reflux, and retrosternal pain[2,3]. When reflux invades the mouth, this can cause soft tissue damage, erosive dental lesions[4], and exposure of dentin often causes painful symptoms[5]. GERD occurs not only after surgery, but also in the non-surgical population.

A large number of previous studies have confirmed that gastroesophageal reflux leads to the destruction of esophageal epithelial barrier function; however, the specific mechanism is still not completely clear. Gastroesophageal reflux leads to the destruction of esophageal epithelial barrier function by regulating the expression and distribution of tight junction proteins (such as Occludin, Cldn1, Cldn3 and Cldn4), reducing the number of desmosomes, and the direct hydrolisis of adhesive junction proteins (such as E-cadherin). This is manifested by the widening of intercellular spaces (ICS) and the reduction of trans-epithelial electrical resistance (TEER)[6-11]. In addition, this is accompanied by an inflammatory response in the mucosal epithelium[12].

Nuclear factor-kappa beta (NF-κB) is an important transcription factor associated with inflammation, which regulates apoptosis, viral replication, tumor formation and autoimmunity in addition to the inflammatory response. Reflux can directly stimulate the esophageal epithelium to recruit a large number of inflammatory cells, activate NF-κB and release inflammatory chemokines (such as interleukin (IL)-1β, IL-6 and IL-8). The up-regulated inflammatory factors and inflammatory cells in turn further activate NF-κB expression in esophageal epithelium[13]. Several clinical studies have shown that NF-κB and related inflammatory factors IL-1β and IL-8 are up-regulated in GERD esophageal mucosa [14-18]. Compared with traditional medications and surgical intervention, targeting NF-κB-mediated esophageal epithelial barrier injury may be a more effective treatment for GERD. It can not only effectively relieve symptoms, but also significantly reduce the side effects caused by medications. Unfortunately, there are few reports on this issue.

Our previous study suggested that the activation of NF-κB in esophageal mucosa may be responsible for the interruption of epithelial barrier function caused by reflux. NF-κB can be activated by different stimuli and is considered to be part of the systemic stress response. Based on the literature and our previous study results[19-28], it can be hypothesized that inhibition of NF-κB activation may block the damage to the esophageal mucosal barrier caused by GERD. To prove this theory, we plan in conjunction with in vitro experiments and an animal study to further elucidate the role of NF-κB in the mechanism of reflux-induced esophageal epithelial barrier dysfunction, and explore the effectiveness of specific inhibition of NF-κB activity on reflux-induced esophageal epithelial barrier dysfunction. This alternative therapeutic approach may be a superior intervention for GERD than traditional treatment. The completion of this study will not only further reveal the molecular pathogenesis of esophageal mucosal injury caused by GERD, but also provide a theoretical and experimental basis for the establishment of new treatment methods for GERD.

**LITERATURE SEARCH**

We conducted a descriptive review of the mechanism associated with GERD in relation to NF-κB. PubMed was searched for articles published from July 1966 to February 2022, using the following MeSH or free-text key words: GERD, NF-κB, pathogenesis, mechanism, inflammatory injury, and esophageal epithelial barrier. The search was limited to papers written in English, with no restrictions on the type of
PATHOGENESIS OF ESOPHAGEAL MUCOSAL INJURY CAUSED BY GASTROESOPHAGEAL REFLUX DISEASE

GERD is a disorder caused by the retrograde flow of reflux into the esophagus. The pathogenesis of GERD involves the interaction of chemical, mechanical, psychological and neural mechanisms (Figure 1).

REFLUX MECHANISM

The reflux insult to esophageal mucosa is the most important pathophysiological mechanism of GERD [29]. However, the components of refluxate are diverse, and include gastric acid, bile acid, and pepsin [30]. Each component has its unique destructive mechanism on the esophageal defense system and consequential impact. GERD is often thought of as acid reflux, where acid refers to hydrochloric acid (HCl) [30], which is a very destructive substance. At the cellular level, the damage caused by HCl to esophageal mucosa is partly due to its influence on the potential difference of esophageal mucosa, which leads to the loss of integrity of epithelial cells and degeneration and necrosis of these cells[31]. In the presence of an acid pocket and hiatal hernia, this increases the exposure time of the esophagus to acidic conditions and is more likely to lead to GERD[32]. However, some patients were found to have a transient elevation in pH up to 7.0 when esophageal pH was tested, indicating the possible presence of alkalinizing agents[33]. Some studies have shown that there is a correlation between bile acid concentration and elevated pH[34]. Under the action of acids, bile acids become lipophilic and can dissolve cell membranes, thus destroying the integrity of the cell after passing through the membrane. It has also been shown to increase the absorption of hydrogen ions in esophageal tissue[35], and the higher the bile concentration, the more esophageal epithelial cells are exposed to this environment, and severe injury can be expected[36]. Bile acid stimulates the release of various inflammatory factors, suggesting that it may have a direct insult on the esophagus[36]. Pepsin, as a peptidase, has a wide range of protein-substrate properties and its release into the esophagus and adjacent structures can cause injury to the surrounding tissues. Unlike the gastrointestinal tract, the esophagus lacks a layer of mucus to protect itself from pepsin digestion and cannot prevent digestion by raising its pH[37]. Thus, pepsin can be activated in the esophagus, leading to cell injury either directly or indirectly[38,39].

MECHANISM OF ESOPHAGEAL CLEARANCE REDUCTION

When the refluxate enters the esophagus, the esophageal mucosa cannot create the necessary biochemical environment to neutralize the reflux due to the lack of mucous secreting cells and bicarbonate production. In order to reduce the exposure time of the esophageal mucosa to reflux, the clearance mechanism is particularly important. Therefore, it can be speculated that a reduction in esophageal clearance rate will lead to GERD, which is supported by previous literature[40]. The factors affecting esophageal clearance include chemical and mechanical mechanisms, such as glandular secretion and esophageal motility pattern. Salivary secretion can affect esophageal clearance through neutralization of acid. It has been suggested in the literature that reduced salivary gland secretion due to other factors is associated with the development of GERD. The relationship between esophageal dysmotility and GERD is a bidirectional influence. Esophageal motor dysfunction and lower esophageal sphincter (LES) relaxation lead to prolonged indwelling of reflux in the esophagus and reduced clearance rate[41,42], subsequently leading to GERD.

GRADIENT MECHANISM OF GASTROESOPHAGEAL REFLUX

Based on anatomy, the major portion of the esophagus is located in the thoracic cavity, and the pressure in the thoracic cavity is lower than that in the abdominal cavity. The maintenance of tension in the LES plays a crucial role in preventing reflux from entering the esophagus. The LES no longer maintains its tension due to external causes such as obesity, hiatal hernia, low tension in the LES itself, or elevated pressure in the abdominal cavity, resulting in reflux into the esophagus and the development of GERD [43,44]. As a related factor, shorter abdominal cavity length was found to cause more reflux[45], which may also be related to the formation of a pressure gradient.
CORRELATION BETWEEN GERD AND NF-κB

The esophageal mucosal barrier is mainly composed of esophageal mucosal epithelial cells. The defensive barrier structure of esophageal epithelium is mainly composed of the apical junctional complexes (AJCs) of esophageal keratinocytes and epithelial cell membrane, which is responsible for preventing luminal ions (mainly hydrogen ions) and small molecules from entering the submucosa[46]. The cell AJCs consist of tight junctions, adherent junctions and desmosomes[47,48]. The esophageal epithelial barrier function mainly involves TEER, the permeability of mucosal epithelium to neutral small molecules and the ICS. A lower TEER value of the same type of epithelial tissue in the same area indicates that the mucosal permeability to ions is stronger, and the mucosal defense barrier function is weaker. GERD activates inflammation when the epithelial barrier is disrupted, and NF-κB is an important transcription factor associated with inflammation[49,50]. Reflux can directly stimulate the esophageal epithelium to produce inflammatory cytokines, up-regulate NF-κB expression, and release inflammatory chemokines such as IL-1β, IL-6 and IL-8. Changes in the microenvironment in turn activate NF-κB to form a positive feedback[11]. As previously discussed, a large number of clinical studies have shown that GERD esophageal epithelium NF-κB and related inflammatory factors are up-regulated. NF-κB can directly regulate tight junction protein expression and impair epithelial barrier function by relaxing tight junctions[51-53]. Previous animal studies have also shown that NF-κB pathway inhibitors can significantly prevent destruction of the reflux-induced esophageal mucosal barrier[44]. During reflux, TEER decreases, which can be offset by the use of inhibitors. Similarly, IL-1β and IL-6 were significantly reduced after the use of NF-κB inhibitors. In another animal model of GERD, a specific inhibitor of NF-κB was also used[20]. Compared with the control group, the inhibitor increased the pH of the distal esophagus, alleviated esophageal mucosal tissue injury and inhibited the inflammatory response, suggesting that NF-κB is a potential therapeutic target for GERD. In addition, in several animal studies using drugs that inhibit the NF-κB pathway, mucosal damage was significantly reduced compared with the control group, and the release of inflammatory factors was reduced as well as oxidation[21-24]. In an in vitro study, lipopolysaccharide (LPS)-induced inflammatory responses in RAW 264.7 cells were also found to be alleviated after treatment with drugs that inhibited the NF-κB pathway[25-26]. These studies suggest that drugs which inhibit the NF-κB pathway can relieve esophageal mucosal injury caused by GERD and down-regulate related inflammatory factors.

In our previous study, we established a mouse model of gastroesophageal reflux and found that injury of the epithelial barrier of reflux esophageal mucosa was associated with NF-κB-mediated inflammation. However, an esophageal perfusion model in rabbits (acid/bile salt was directly injected into the rabbit esophageal cavity through a catheter) suggested that damage to the epithelial barrier function of esophageal mucosa was related to direct chemical injury by reflux. Also, by comparing the above two studies, it was found that acid reflux did not cause obvious injury and inflammation to the esophageal mucous membrane epithelium in mice, but caused obvious damage and inflammation to the esophageal mucosa in rabbits[31]. These differences may be due to the fact that the esophageal mucosa of rodents (e.g., mice and rats) is coated with hyper-keratinized laminated squamous epithelium, which is highly

Figure 1 Mechanisms of gastroesophageal reflux.
resistant to acid. The esophageal mucosa of rabbit is similar to that of humans, and is covered with incomplete keratinized lamellar squamous epithelium and has poor resistance to acid. In conclusion, we propose that the reduction of esophageal mucosal barrier function induced by gastroesophageal reflux may be the result of a combination of direct chemical destruction and a NF-κB-mediated inflammation process.

The treatment of GERD has many challenges. First, the pathogenesis of GERD has not been completely clarified[54,55]. Although research has made progress in recent years, consensus results have not been established in the literature. However, the incidence of GERD is high and the impact on patients’ quality of life is significant. Second, as mentioned above, traditional therapies are flawed and there is a lack of effective targets for treatment. Third, although the relationship between GERD and NF-κB is well documented and NF-κB inhibitors have only been shown to be effective in animal studies, more investigations are warranted to improve their clinical application.

CONCLUSION
As one of the most common chronic disorders, the symptoms of GERD can be variable, and include non-cardiogenic chest pain, chronic cough, hoarseness, globular and throat irritation[56]. NF-κB activation plays an important role in the development of GERD. However, there is limited information on the treatment of GERD via this pathway. NF-κB is a well-known transcription factor involved in inflammation and cell proliferation. If research is able to demonstrate the benefit of altering NF-κB level in the development of GERD, it would have an enormous impact on GERD treatment in clinical practice.

FOOTNOTES
Author contributions: Zhang ML and Ran LQ contributed equally to this work. They edited the article together; Wu MJ provided writing guidance for this paper; Jia QC collected and organized the articles; Yong GP polished the language of the article; Qin ZM determined the propositional direction of the article; all authors have read and approved the final manuscript.

Conflict-of-interest statement: There is no conflict of interest in this article.

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S-Editor: Ma YJ
L-Editor: Webster JR
P-Editor: Ma YJ

REFERENCES
5 Lussi A, Schlueter N, Rahktamullina E, Ganss C. Dental erosion--an overview with emphasis on chemical and histopathological aspects. Caries Res 2011; 45 Suppl 1: 2-12 [PMID: 21625128 DOI: 10.1159/000325915]
Zhang ML et al. NF-κB: Pathway for treatment of GERD?

10.1053/gast.1996.v111.pm889633


8 Oshima T, Koseki J, Chen X, Matsumoto T, Miwa H. Acid modulates the squamous epithelial barrier function by modulating the localization of claudins in the superficial layers. Lab Invest 2012; 92: 22-31 [PMID: 21912379 DOI: 10.1038/labinvest.2011.139]


Nam L, Nam HH, Park BY, Kim BT, Choo BK. Ameliorative effects of Magnolia sieboldii buds hexane extract on experimental reflux esophagitis. Phytother Res 2020; 34: 2385-2396 [PMID: 32255235 DOI: 10.1002/ptr.6689]


Nam HH, Nan L, Choo BK. Anti-Inflammation and Protective Effects of Anethum graveolens L. (Dill Seeds) on Esophageal Mucosa Damages in Reflux Esophagitis-Induced Rats. Foods 2021; 10 [PMID: 34681549 DOI: 10.3390/foods10122500]


Zhang ML et al. NF-κB: Pathway for treatment of GERD?

1981; 68: 286-293 [PMID: 6788804 DOI: 10.1172/jci110246]


38 Johnston N, Knight J, Dettmar PW, Lively MO, Koffman J. Pepsin and carbonic anhydrase isozyme III as diagnostic markers for laryngopharyngeal reflux disease. Laryngoscope 2004; 114: 2129-2134 [PMID: 15564833 DOI: 10.1097/01.mlg.0000149445.07146.03]


53 Al-Sadi RM, Ma TY. IL-1beta causes an increase in intestinal epithelial tight junction permeability. J Immunol 2007; 178: 4641-4649 [PMID: 17372023 DOI: 10.4049/jimmunol.178.7.4641]


Obligate aerobic, gram-positive, weak acid-fast, nonmotile bacilli, *Tsukamurella tyrosinosolvens*: Minireview of a rare opportunistic pathogen

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**Abstract**

*Tsukamurella* species are obligate aerobic, gram-positive, weak acid-fast, nonmotile bacilli. They are found in various environments, such as soil, water, sludge, and petroleum reservoir wastewater, and belong to the order *Actinomycetales*. In 2016, there was a reclassification of species within the genus *Tsukamurella*, merging the species *Tsukamurella tyrosinosolvens* (*T. tyrosinosolvens*) and *Tsukamurella carboxydivorans*. *Tsukamurella* species are clinically considered to be a rare opportunistic pathogen, because most reported cases have been related to bacteremia and intravascular prosthetic devices and immunosuppression. To date, it has been isolated only from human specimens, and has always been associated with clinical disease; human infections are very rare. Reported infections have included pneumonia, brain abscesses, catheter-related bloodstream infections, ocular infections, bacteremia, and sepsis presenting with septic pulmonary emboli in patients who are immunocompromised. To date, there is no commercially available test for identification. On the other hand, sequence-based identification, including matrix-assisted laser desorption ionization time-of-flight mass spectrometry, is an alternative method for identifying clinical isolates that are either slow growers or difficult to identify through biochemical profiling. The golden standards for diagnosis and optimal management still remain to be determined. However, newer molecular biological techniques can provide
accurate identification, and contribute to the appropriate selection of definitive therapy for infections caused by this organism. Combinations of several antimicrobial agents have been proposed for treatment, though the length of treatment for infections has yet to be determined, and should be individualized according to clinical response. Immunocompromised patients often experience severe cases due to infection, and life-threatening T. tyrosinosolvens events associated with dissemination and/or failure of source control have occurred. Favorable prognoses can be achieved through earlier identification of the cause of infection, as well as successful management, including appropriate antibiotic therapy together with source control. Further analyses of similar cases are required to establish the most adequate diagnostic methods and treatment regimens for infections.

Key Words: Tsukamurella tyrosinosolvens; Gram-positive bacilli; Opportunistic infection; Sequence-based identification; Matrix-assisted laser desorption ionization time-of-flight mass spectrometry; Combination antibiotic therapy

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Core Tip: Tsukamurella species are obligate aerobic, gram-positive, weak acid-fast, nonmotile bacilli that are found in various environments, including soil, water, sludge, and wastewater from petroleum reservoirs; these nonmotile bacilli are obligate aerobic, gram-positive, and weak acid-fast [1-4]. They were initially isolated from bedbug mycetoma and ovaries, in 1941 [5]. The name Tsukamurella comes from Tsukamura and Mizuno [6], the microbiologists who described the first Gordona aurantica strain in 1971, which had been isolated from the sputum of a patient suffering from a chronic lung pathology [5-7]. The genus Tsukamurella currently contains 12 species with validly published names that include Tsukamurella tyrosinosolvens (T. tyrosinosolvens) and Tsukamurella carboxydivorans. To date, human infections are very rare, and reported infections include pneumonia, brain abscesses, cathereter-related bloodstream infections, ocular infections, and bacteremia in patients who are immunocompromised. The golden standards for diagnosis and optimal management still remain to be determined. Immunocompromised patients often experience severe cases due to infection, and life-threatening T. tyrosinosolvens events associated with dissemination and/or failure of source control have occurred. Favorable prognoses can be achieved through earlier identification of the cause of infection, as well as successful management, including appropriate antibiotic therapy together with source control. Further analyses of similar cases are required to establish the most adequate diagnostic methods and treatment regimens for infections.

INTRODUCTION

Tsukamurella species, which are members of the order Actinomycetales, can be found in a variety of different environments, including soil, water, sludge, and wastewater from petroleum reservoirs; these nonmotile bacilli are obligate aerobic, gram-positive, and weak acid-fast [1-4]. They were initially isolated from bedbug mycetoma and ovaries, in 1941 [5]. The name Tsukamurella comes from Tsukamura and Mizuno [6], the microbiologists who described the first Gordona aurantica strain in 1971, which had been isolated from the sputum of a patient suffering from a chronic lung pathology [5-7]. The genus Tsukamurella currently contains 12 species with validly published names that include Tsukamurella tyrosinosolvens (T. tyrosinosolvens), and was first described by Collins et al [8] in 1988. Following a 2016 reclassification of Tsukamurella species, the species T. tyrosinosolvens and Tsukamurella carboxydivorans have been merged [4]. The genus is phylogenetically related to other mycolic acid-containing genera of the order Actinomycetales, including Nocardia, Gordonia, Streptomyces, Rhodococcus, Corynebacterium, and Mycobacterium, because of their similar phenotypic properties [1,7,9,10].

ROUTE OF INFECTION AND SYMPTOMS

Tsukamurella species infections are rare in humans, as the species is a type of saprophyte bacterium [5]. This genus has the potential to cause various infections in humans, and more and more infections have been reported in Asia, America, Europe, and Africa, suggesting a global emergence of diseases caused...
Tsukamurella spp. are clinically considered a rare opportunistic pathogen, as most reported cases have been related to bacteremia and intravascular prosthetic devices, such as catheters or cardiac pacemaker implants, and immunosuppression (hematological malignancy, post chemotherapy, chronic renal failure, graft-versus-host disease after bone marrow transplant, and acquired immunodeficiency syndrome)[1,2,12-14]. Catherer-related infection range varies, from infections of the local insertion site to metastatic deep-seated infections[9]. In addition, a case has been reported of a septic pulmonary embolism, secondary to a central venous catheter-related bloodstream infection (CRBSI)[15]. Other examples include cutaneous infection, meningitis, brain abscesses, lung infection, peritonitis, knee prosthesis infection, and ocular infection[2,11,16]. Among these, a striking similarity has been noted between the clinical features of lung disease with Tsukamurella and those of mycobacterial infections[16]. There is a great likelihood that Tsukamurella lung disease incidence is significantly underestimated in areas with high tuberculosis incidence rates; it is conceivable that Tsukamurella has greater community prevalence than currently recognized[16].

To date, T. tyrosinosolvens has been isolated only from human specimens, and has been associated with clinical disease in all cases; human infections are very uncommon[7]. The infections reported have included pneumonia, brain abscesses, CRBSI, ocular infections, bacteremia, and sepsis presenting with septic pulmonary emboli[1,7,14,17].

On the other hand, there has been a reported case of coinfection with T. tyrosinosolvens and another microorganism (e.g., Mycobacterium bovis pneumonia) in an immunocompromised patient[17].

EXAMINATIONS

To date, no test to identify Tsukamurella spp. is commercially available[7]. The genus bears a phylogenetic relation to other Nocardia, Gordonia, Streptomyces, Rhodococcus, Corynebacterium, Mycobacterium, and other mycotic acid-containing genera of the order Actinomycetales; because of similarities in their phenotypic properties, it remains difficult for the majority of clinical microbiology laboratories to identify individual species using ordinary biochemical tests[1,9,10,18]. As a result, identification using conventional biochemical assays has proven unsuccessful, and it is not feasible to accurately identify Tsukamurella through phenotypic methods[1,7,11]. Here, to help share a better understanding of this pathogen through our experience, we show gram staining of T. tyrosinosolvens from aerobic bottles, in blood cultures from a blood sample of a CRBSI patient at our institution (× 1000 magnification). Numerous rod-shaped bacteria are confirmed (Figure 1). We also show colonies of T. tyrosinosolvens on a blood agar plate, in a blood sample from a CRBSI patient at our institution. This confirmed the development of flat, huge, dry, and white- to light-cream-colored colonies, in addition to crow’s feet in the overlapping portions (Figure 2).

One alternative method for identifying clinical isolates that are either slow growers or difficult to identify through biochemical profiling is sequence-based identification[7]. Because clinical laboratories most frequently use the 16S rRNA gene as a target for molecular identification, and for the identification of unusual pathogens, sequencing serves as a comparatively rapid and reliable new molecular technique[1,7,13,18]. Previous studies have shown that the majority of Tsukamurella species have highly similar 16S rRNA gene sequences in common (> 99% nucleotide identities); as a result, these species cannot be confidently identified using this gene target[18]. Despite this, 16S rRNA gene sequences have been found to be insufficiently discriminatory for the purpose of identifying certain species, including Tsukamurella species, due to the minor differences that exist within various Tsukamurella species’ 16S rRNA gene sequences[1,7,9]. However, in previously reported criteria used to interpret partial 16S rRNA gene sequences, the sequence provided 100% identification for T. tyrosinosolvens (GenBank Accession numbers AY238514, Y12246, Y12245, and Y12247)[9].

An isolate digested by HinfI (440 bp) and MspI (313/135 bp) leaves unique fragments compatible with Tsukamurella species identification[1]. Other bacterial genera have been successfully identified through other gene targets, including ssrA (stable small RNA), secA (the secretion ATPase), rpoB (beta-subunit of RNA polymerase), and groEL (heat shock protein 60)[5,18,19]. On the other hand, the groEL gene is reportedly useful for speciation of T. tyrosinosolvens[1,11]. However, two gene sequences for Tsukamurella species were found to be available within the GenBank database: T. tyrosinosolvens (GenBank accession No. U90204) and T. panrometabola (GenBank accession No. AF352578)[1]. This indicates that further studies of groEL gene sequencing of multiple strains of each Tsukamurella species would be merited, as verification of suitability for speciation of Tsukamurella[1,11]. Furthermore, regarding the biodegradation of hydrocarbons, two alkane catabolic pathways have been discovered within the T. tyrosinosolvens PS2 genome, unlike the above-mentioned representatives of the genus Tsukamurella[4]. One of these pathways contains an alkane 1-monoxygenase gene (alkB; GenBank accession number KZ197795), two rubredoxin genes (rubA; GenBank accession numbers KZ197794 and KZ197793), one rubredoxin-reductase gene (rubB), and one regulatory protein TetR gene (alkU; GenBank accession number KZ197792)[4]. This pathway resembles that of the alkane-degrading actinomycete T. tyrosinosolvens strain MH1, in accordance with the complete genome[4]. In addition, a gene known to perform a key alkane degradation role was found within the T. tyrosinosolvens PS2 genome (GenBank
accession number KZL95198), homologous to cytochrome P450 alkane 1-monoxygenase, from the Gordonia spp. strain TF6 (GenBank accession number BAF95905)[4]. Consequently, these two systems may benefit this particular strain in highly polluted environments, and may additionally offer insights into the ecological role played by this bacterium[4].

PCR sequencing is not yet used in clinical laboratories as a routine method of identification, due to its expensive, time-consuming nature and its technical demands[11]. To date, none of the 60 isolates have been correctly identified at the species level using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) with the original Bruker database V.6.0.0.0[11]. By using the Bruker database, expanded with 15 type and reference strains that cover all 11 Tsukamurella species recognized to date, 59 of the 60 isolates were accurately identified at the species level, with scores of ≥ 2.0[11]. Therefore, MALDI-TOF MS should prove beneficial for the routine identification of Tsukamurella species in clinical microbiology laboratories, once the database has been optimized[11]. However, because of its inability to correctly identify species of Tsukamurella, it is necessary to continually expand the MALDI-TOF MS databases to add more gram-positive rods[11]. Tsukamurella isolates have also been identified at the species level through PCR-restriction fragment length polymorphism analysis, as well as through 16S rRNA gene sequencing[1,7,20,21]. One identification scheme based on PCR-restriction fragment length polymorphism, using an amplified 440-bp segment of hsp65, has been described as being performed with the primers TB11 (5’-ACCAACGATGGTGTGTCCAT-3’) and TB12 (5’-CCTGTGAACCGGATACCCCT-3’) [1].

Regarding other genetic analysis, it has been confirmed through DNA-DNA hybridization that these are distinct from the other known species within the genus Tsukamurella (26.2% ± 2.4% to 36.8% ± 1.2% DNA-DNA relatedness), in line with results of in silico genome-to-genome comparison (32.2%-40.9% Genome-to-Genome Distance Calculator and 86.3%-88.9% average nucleotide identity values)[19].
DIAGNOSIS

For diagnoses, physicians should ask for detailed information about patients’ working and living environments, as well as their histories of animal contact, and perform routine bacterial smear tests[16]. The first step towards a reliable diagnosis of Tsukamurella infections is a high level of suspicion, and a low threshold for microbiological sampling[16]. Ideally, molecular diagnostic assays should serve as the routine laboratory method[16]. Given the rising number of Tsukamurella infections, new Tsukamurella species implementations in matrix-assisted laser desorption ionization time-of-flight databases need to be more discriminant[22].

TREATMENT

The optimal management of Tsukamurella bacterial infections has yet to be determined[1]. Based on treatment principles for nocardiosis and atypical mycobacterial infections, a number of combinations of antimicrobial agents have been proposed as potential treatments for Tsukamurella infections[1,5]. To date, there remains no recommended standard susceptibility method for Tsukamurella species; however, in most case reports, a susceptibility to amikacin, clarithromycin, imipenem, ciprofloxacin, and trimethoprim-sulfamethoxazole has been noted in Tsukamurella isolates, as well as a resistance to penicillin, cefotaxin, and expanded-spectrum cephalosporins, determined through a standard in vitro antibiotic disk diffusion susceptibility assay[1,9]. Immunocompromised patients often experience severe cases due to infection, and life-threatening T. tyrosinosolvens events associated with dissemination and/or failure of source control have occurred[14,15]. Favorable prognoses can be achieved through earlier identification of T. tyrosinosolvens as the cause of infection, as well as successful management, including appropriate antibiotic therapy with source control[9,14]. In particular, good clinical outcomes are possible for CRBSI caused by Tsukamurella species, through a combination of appropriate antibiotics and catheter removal; this is likely to be the most effective management strategy for patients[1,2,9].

The length of treatment for Tsukamurella bacterial infections has yet to be determined, and should be individualized based on clinical response[1]. On the other hand, expect frequent relapses, especially in hosts who are immunocompromised; it is recommended to administer prolonged antibiotic treatment and oral suppressive treatment[1,17].

INFECTION CONTROL

Multiple lapses in infection control have been identified; the most likely cause of the outbreak was the clinic improperly preparing the saline flush syringes[23]. It has been demonstrated, through this outbreak, that oncology patient bloodstream infections can be the result of improper infection control practices; this serves to highlight the critical necessity of increased attention to, and supervision of, infection control measures in outpatient oncology settings[23].

CONCLUSION

This mini-review aims to highlight the difficulty of identifying the genus Tsukamurella. The golden standards for diagnosis and optimal management still remain to be determined. However, accurate identification can be achieved through newer molecular biological techniques, thus contributing to appropriate selection of definitive therapy for infections due to this organism. Further analysis of similar cases is required in order to establish the most adequate diagnostic methods and treatment regimens for T. tyrosinosolvens infections. In addition, future studies should aim to establish better guidelines for the effective management of Tsukamurella infections.

FOOTNOTES

Author contributions: Usuda D wrote the manuscript; Tanaka R, Suzuki M, Shimozawa S, Takano H, Hotchi Y, Tokunaga S, Osugi I, Katou R, Ito S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Oba J, Nomura T and Sugita M proofread and revised the manuscript; all authors approved the final version to be published.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

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S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

REFERENCES


19 Teng JLL, Fong JYH, Fok KMN, Lee HH, Chiu TH, Tang Y, Ngan AHY, Wong SSY, Que TL, Lau SKP, Woo PCY. Tsukamurella asaccharolytica sp. nov., Tsukamurella conjunctivitidis sp. nov. and Tsukamurella sputi sp. nov., isolated from patients with bacteraemia, conjunctivitis and respiratory infection in Hong Kong. Int J Syst Evol Microbiol 2020; 70: 995-1006 [PMID: 31738158 DOI: 10.1099/ijsem.0.003861]


Diffusion tensor imaging pipeline measures of cerebral white matter integrity: An overview of recent advances and prospects

Amanina Ahmad Safri, Che Mohd Nasril Che Mohd Nassir, Ismail Nurul Iman, Nur Hartini Mohd Taib, Anusha Achuthan, Muzaimi Mustapha

Abstract

Cerebral small vessel disease (CSVD) is a leading cause of age-related microvascular cognitive decline, resulting in significant morbidity and decreased quality of life. Despite a progress on its key pathophysiological bases and general acceptance of key terms from neuroimaging findings as observed on the magnetic resonance imaging (MRI), key questions on CSVD remain elusive. Enhanced relationships and reliable lesion studies, such as white matter tractography using diffusion-based MRI (dMRI) are necessary in order to improve the assessment of white matter architecture and connectivity in CSVD. Diffusion tensor imaging (DTI) and tractography is an application of dMRI that provides data that can be used to non-invasively appraise the brain white matter connections via fiber tracking and enable visualization of individual patient-specific white matter fiber tracts to reflect the extent of CSVD-associated white matter damage. However, due to a lack of standardization on various sets of software or image pipeline processing utilized in this technique that driven mostly from research setting, interpreting the findings remain contentious, especially to inform an improved diagnosis and/or prognosis of CSVD for routine clinical use. In this minireview, we highlight the advances in DTI pipeline processing and the prospect of this DTI metrics as potential imaging biomarker for CSVD, even for subclinical CSVD in at-risk individuals.
Key Words: Diffusion tensor imaging; White matter; Cerebral small vessel disease; Pipeline processing; Tractography

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Core Tip: Cerebral small vessel disease (CSVD) is a leading cause of age-related microvascular cognitive decline resulting in significant impairment. Despite the general acceptance of key terms from neuroimaging findings as observed on the magnetic resonance imaging (MRI), key questions on CSVD remain elusive. The MRI-based diffusion tensor imaging (DTI) offers non-invasive tool to quantitate brain white matter connections via fiber tracking that may inform the extent of CSVD-associated white matter damage. In this minireview, we highlight the advances in DTI pipeline processing and the prospect of DTI metrics as potential biomarker for CSVD amenable towards a routine clinical use.

INTRODUCTION

Cerebral small vessel disease (CSVD), in its prevalent sporadic form, refers to a syndrome of clinical and neuroimaging findings in ageing populations that is frequently related to vascular risk factors and onset of neurological impairments including stroke, dementia, parkinsonism, gait problems, and mood disturbances[1,2]. Sporadic CSVD pathologies are often heterogeneous, as evidenced by neuroimaging findings such as lacunes, white matter hyperintensities and enlarged perivascular spaces on T2-weighted magnetic resonance imaging (MRI)[3,4]. While conventional MRI and MRI-based diffusion-weighted imaging (DWI) provide a detailed picture of the overall severity of white matter involvement, it is only capable of measuring diffusion in a single direction[5]. Therefore, improved relationships and reliable lesion studies are desired to enhance the assessment of white matter architecture and connectivity such as white matter tractography using diffusion-based MRI (dMRI)[6,7].

Within dMRI, diffusion tensor imaging (DTI) offers data that can be used to explain brain white matter connections non-invasively through fiber tracking[8]. One of the more current improvements in DTI is the advancement of models of individual patient-specific white matter tracts, namely the diffusion tensor tractography, which is thought to be suitable to examine the effect of CSVD on white matter tracts[9]. Various sets of computerized software or image pipeline processing (i.e., from dMRI data capture to image processing and data interpretation) are used along the process due to a lack of standardization and variability in the reported findings[10]. As we strive to better understand this complex condition, this mini review will summarise the recent advances and prospects of DTI pipeline application for the clinical detection and assessment of the cerebral white matter integrity.

CSVD- AN OVERVIEW

CSVD is widely recognised as a neurovascular syndrome featuring clinical, cognitive, neuroimaging, and neuropathological findings that arise from damage and disruption involving a complex neurogliovascular unit in the brain[11-13]. Due to various vascular-pathologic developments that could disrupt the perforating cerebral capillaries and arteries that supply the brain subcortical region with restricted collaterals, parenchymal damage is seen in the grey and deep white matter of the subcortical area (as shown in Figure 1)[14-16]. Consequently, CSVD imposes a significant impact on neuropsychological function as well as common neuropathological processes, and contributes significantly to development of cognitive impairment, dementia, and stroke[17-20]. Moreover, conventional vascular risk factors such as hypertension, diabetes, hyperlipidaemia and smoking have been shown to increase the risk towards development and progression of CSVD[21]. There are two main forms of CSVD which includes amyloidal CSVD [sporadic and hereditary cerebral amyloid angiopathy] and non-amyloidal CSVD (age-related and vascular risk-factor-related small vessel, i.e., arteriolosclerosis)[22]. CSVD is commonly ascribed to a series of neuroimaging manifestations, consisting of recent small subcortical infarcts, lacunes, white matter hyperintensities (WMHs), cerebral microbleeds, prominent or enlarged perivascular spaces, cortical microinfarcts, and atrophy[3,23,24]. Figure 2 shows key manifestations of...
Figure 1: Illustration of cerebral vasculature and general pathophysiology of cerebral small vessel disease. Different branches of cerebral arteries and their territories supplying the cerebral white matter: (1) cortical arteries, (2) pial arterioles that supply deep white matter, (3) short branches of anterior choroidal arteries that branch into sub-ependymal arteries, arterioles of sub-ependymal, and (4) middle cerebral artery (MCA) that branches into thalamic and lenticulostriate perforating arteries. The picture also shows branches of MCA penetrate the subcortical region of white matter and grey matter. In cerebral small vessel disease (CSVD), a thromboembolism in the MCA eventually occludes the lenticulostriate arteries, resulting in a lacunar lesion in basal ganglia. If the atheroma in the parent artery is positioned at the opening of its penetrating branches, it could lead to an acute occlusion of one or several penetrating arteries hence causing a lacunar infarct. A more extensive small vessel disease may lead to a diffused disruption of the blood-brain barrier [3]. ACA: Anterior Cerebral Artery; MCA: Middle Cerebral Artery; ICA: Internal Carotid Artery.

CSVD as streamlined for CSVD research/practical purposes by the standards for reporting and imaging of small vessel disease (STRIVE) [25]. Hence, DTI can provide a powerful insight into white matter integrity and damage found in CSVD, thus providing a possible marker for disease severity and relatable to CSVD symptoms and/or signs that would otherwise go undetected using conventional MRI [26].

DTI

DTI is a non-invasive dMRI-based method for visualizing tissue macro- and microstructures for pathological evaluation. Based on the microstructural features (e.g., fiber diameter, fiber density, and myelination) that limit perpendicular diffusion and restrict water movement in specific directions, DTI assesses the free movement of water molecules inside the white-matter tracts [27]. Isotropic diffusion occurs when there are no barriers in their path, such as in a beaker of water, where molecules bumping around due to thermal action will scatter in the same way. When molecules encounter oriented barriers, however, movement is no longer dispersed evenly along all paths, and diffusion becomes anisotropic [28].

The use of DTI as a visualization tool has helped to distinguish between large, oriented macro-molecule structures such as the brain white matter fiber bundles [29]. DTI tractography not only allows for the mapping of fiber tracts that are characteristic of the fundamental anatomy, but it also allows for the testing of hypotheses about age-related changes in white matter structure, as well as the distance of specific fiber tracts.

PRINCIPLE OF DTI – THEORY TO PRACTICES

The DTI parameter is reliant not entirely on static magnetic strength field, but rather on the signal-to-noise ratio (SNR) and impact of the artifact. The MRI platforms with 1.5T and 3T magnetic field strength are commonly used in routine DTI human brain scanning, although some centres have access to the 7T platform. It is acknowledged that scanning with a higher field strength improves the SNR, which equates to better results [30,31]. Aside from static magnetic fields, the number, power, and gradient coils also contribute significantly to the value of DTI data. The gradient task cycle verifies the methods for
obtaining 2D images for each repetition time. The most recent scanners offer longer task cycles, allowing data to be stored in less time. Gradient force improvement allows for greater dispersion weighting and interpretation in a shorter time frame. This implies that the echo time can be reduced sequentially. Reducing the sensitivity effects will subsequently improve information conditions. Moreover, a high slew rate is desirable for DTI[6]. Nonetheless, the rapid growth and collapse of a strong gradient can cause picture-distorting eddy currents and mechanical vibrations, as well as peripheral nerve stimulation, which may result in patients' spontaneous muscle cramps. A clinical system operating for the maximum gradient amplitude is typically 40-80 milliTesla/meter (mT/m) plus 150-200 mT/m for each millisecond highest slew rate for safety reasons[32].

Non-standard apparatus offered by imaging manufacturers or built by and for investigation could improve DTI files. Using multichannel phased array coils instead of birdcage coils to improve SNR and allow equivalence scanning is a simple way to improve the quality of DTI files. However, an increase in the number of module coils may create a bias area that favors cortical exposure over deep white matter, making DTI in this region less ideal[32,33]. Without quantification, the data cannot be statistically analyzed, and visualization findings cannot be associated with scientific outcomes[34].

Visual evaluation of dMRI images can be validated by vague quantifiable measures taken from DTI files consisting of fractional anisotropy (FA), mean diffusivity (MD), and Trace (Tr). Tr of the diffusion tensor (D) indicates the total water content. Variations in Tr(D) can be recognized uniquely to variations in the formation of tissue[35]. FA calculates the relationship between the magnitude of the anisotropic element of D and the entire magnitude of D. FA values are in the limit of (0 or 1) and can be assessed in each voxel. FA is a commonly applied DTI measure that explains the intensity of diffusion anisotropy in a voxel[36,37].

DTI analyses are classified into three main groups: whole brain, regional and voxel-based methods. An increasing number of software tools are available to analyze DTI information which differ significantly in their purposes. The wide scope of analysis methods and diverse aims in software packages contributes to an absence of consistency that muddles the evaluation of DTI information and understanding the findings[38].

<table>
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<th>CSVD manifestation</th>
<th>Example Image</th>
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</thead>
<tbody>
<tr>
<td>Recent small subcortical infarcts</td>
<td>&lt;20 mm in axial section, hypointense in the T1 sequence, hyperintense in T2 and FLAIR sequences and isointense in GRE-T2 sequence.</td>
<td></td>
</tr>
<tr>
<td>Lacunae of presumed vascular origin</td>
<td>Round or oval subcortical lesions 3–15 mm in diameter, filled with the CSF-like signal; the lesions cavity filled with CSF and surrounded by a hyperintense rim. Isointense in the DWI sequence, hypointense in the FLAIR and T1 sequences, and hyperintense in the T2 sequence.</td>
<td></td>
</tr>
<tr>
<td>White matter hyperintensities</td>
<td>Symmetric regardless of size; hyperintense in the T2, FLAIR and GRE-T2 (gradient-echo T2) sequences; isointense in DWI; and hypointense in T1.</td>
<td></td>
</tr>
<tr>
<td>Enlarged perivascular spaces (Virchow–Robbin spaces)</td>
<td>&lt;2 mm (mostly seen in basal ganglia); hyperintense lesions of the WM and lacunar condition but not brain atrophy; the lesions are hyperintense in T2 sequences, hypointense in FLAIR and T1 sequences, and isointense in the GRE-T2 sequence.</td>
<td></td>
</tr>
<tr>
<td>Cerebral microbleeds (CMBs)</td>
<td>Small, homogenous lesions &lt;10 mm in diameter, characterized by the ‘blooming effect’; best seen in the gradient-echo T2 sequence (hyperintense lesions); isointense in the T2, T1 and FLAIR sequences.</td>
<td></td>
</tr>
<tr>
<td>Brain atrophy</td>
<td>Brain atrophy in the context of CSVD is considered only when the patient has not suffered a stroke or head injury.</td>
<td></td>
</tr>
</tbody>
</table>

DOI: 10.12998/wjcc.v10.i24.8450 Copyright ©The Author(s) 2022.

Figure 2 Several cerebral small vessel disease manifestations according to standards for reporting and imaging of small vessel disease[63]. CSVD: Cerebral small vessel disease; CSF: Cerebrospinal fluid; WM: White matter; DWI: Diffuse-weighted imaging; FLAIR: Fluid-attenuated inversion recovery; GRE: Gradient recalled echo; CMBs: Cerebral microbleeds.
The whole-brain analysis technique is used to find a quantitative DTI measure from all the white matter voxels in the brain and used seed regions from all voxels in the brain[39,40]. Histogram analysis is used to summarize the DTI measured that has been obtained from the chosen voxels of interest which reveals the frequency distribution number of voxels with certain values of the diffusion amount[41,42]. Meanwhile, region-specific analysis techniques are region of interest (ROI) analysis and tractography analysis. ROI is a diffusion measure acquired from a region in a brain that is marked by manual or by automated segmentation or parcellation[43,44]. Whereas the voxel-based analysis (VBA) technique evaluates and compares DTI measurement in the tiniest imaging possible (i.e., the individual voxel)[45]. Fiber tracking or tractography is a post-processing method that can effectively analyze white matter fiber bundles in vivo. Tractography analysis describes the statistical rebuilding of the white matter fiber bundle interpretations by integration of the local diffusion tensor information from each voxel and associated with a riddle “connecting the dots”[46,47]. Tractography is reliant on user input to identify sites in the brain through which tracts are to be rebuilt and that reliant on options are recognized to be anatomically related[48].

CLINICAL APPLICATIONS OF DTI

DTI is applied in a range of clinical situations and is not restricted to neurological purposes. DTI is employed for variable measures in medical procedures even though its efficiency remains primarily a preclinical research device. Currently, the medical use of DTI by probable clinical value is for the preparation of neurosurgical and radiotherapeutic procedures. DTI application not only offers microstructural knowledge on biological location and structure, but also macrostructural information involving the white matter tracts and connections among vital cortical and subcortical functional regions in the brain[49]. Additionally, DTI can provide complementary knowledge about the essential subcortical structure and thus can be utilized in neurosurgical and radiotherapeutic planning. Moreover, DTI is also used in the identification and follow-up of brain tumors[50,51], multiple sclerosis[52], demyelinating disorder, dementia[53-55], psychiatry[56,57] and traumatic brain injury[38].

DIFFUSION TENSOR IMAGING (DTI) PIPELINE ANALYSIS

There are tons of computerized software tools available in the literature with various functionalities, varying from data import, basic image viewing and processing, image quality improvement, registration, automatic segmentation, and DTI tractography to higher-order diffusion modelling and enhanced tractography[38,59-61]. It can be classified into different functions or applications. The general technique in DTI pipeline processing (i.e., a connected series of image processing elements, in which the output becomes the input of the next image processing unit in a pipeline[62] and analysis involves a few steps, including artifacts and data acquisition techniques, quality control and pre-processing, processing and visualization, quantitative analysis, multimodal studies, and lastly the interpretation of results (Figure 3)[63].

Data acquisition is an essential step in DTI pipeline processing. Poor data acquisition can affect data quality and data analysis. Parameters that need to be considered in data acquisition include several diffusion directions, image resolution, b-value, b-value number, and average number. Table 1 shows the minimum required data acquisition parameters in DTI pipeline processing. The framework of the DTI pipeline is pre-processing, tensor estimation and fiber tracking. Due to the inadequate interoperability between the DTI analysis tools and the absence of standard DTI format[64], a lot of software bundles were developed and used to define their data format, such as Neuroimaging Informatics Technology Initiative (NIfTI)[65,66]. File formats such as dcm’i, NIfTI tools, MRicro and software converter package (e.g., Freesurfer, SPM, Splicer) are usually utilized to transform files from the original clinical-setting such as digital imaging and communications in medicine (DICOM) format[66,67]. In tensor estimation, there are three main methods used to estimate tensors which are Linear Least Square (very simple executed in a single-step process, but it depends on hardware, size, and several datasets)[68], Weighted Linear Least Squares (quick method, but it varies on the magnitude of the MRI files e.g., intensities of different DWI)[68] and Non-Linear Least Square (solved over the established system of nonlinear equations, but it also depends on the hardware and size of the dataset and may take minutes up to several hours to produce tensor estimation)[69]. Tools that can be used as tensor estimation are MedInria2[70], DTI Studio[71], Brain Voyager[72], and MRTRix[73].

Fiber tracking is the method for extraction of fiber pathways to quantify the white matter integrity[74]. The software used for fiber tracking includes DTITrack[63], Fiber navigator[70], MedInria2[70], and MRTRix[73]. The quantitative and correlation analysis consists of ROI analysis, VBA, and tract-based spatial statistics (TBSS) will be utilized to extract summary measures from either anatomical regions or the whole brain. In brief, ROI analysis is established on the manual delineation of prior certain regions of the brain or automated parcellations. VBA involved the registration of diffusion maps into a standard space to accomplish correspondences among individuals across voxel and consequently anatomical
Table 1 Minimum requirement of data acquisition in diffusion tensor imaging pipeline processing[84]

<table>
<thead>
<tr>
<th>Data acquisition parameter</th>
<th>Minimum requirement</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field signal</td>
<td>1.5 T or 3T</td>
<td>Give a higher visual score, larger number of fibres. 7T and above = enables identification of smaller anatomical structures</td>
</tr>
<tr>
<td>Number of diffusion direction</td>
<td>Approximate 21</td>
<td>Lowest should be 6 diffusion direction, however it is advice to use more than 6 direction and can go up to 100 directions</td>
</tr>
<tr>
<td>Image resolution</td>
<td>depend on the FOV (usually 24 cm × 24 cm)</td>
<td>Large enough to prevent aliasing</td>
</tr>
<tr>
<td>B-value</td>
<td>0-1000 s/mm²</td>
<td>500-5000+ for HARDI acquisition 2500 for q-space even higher, e.g., 5-8000</td>
</tr>
<tr>
<td>Number of b-values (b = 0) images</td>
<td>2</td>
<td>About 1 per 6 diffusion images</td>
</tr>
<tr>
<td>Number of averages</td>
<td>NSA = 2</td>
<td>Can improve the SNR</td>
</tr>
</tbody>
</table>

T: Tesla; FOV: field of view; HARDI: High angular resolution diffusion imaging; NSA: Number of signal average; SNR: Signal to noise ratio.

Figure 3 Typical diffusion tensor imaging workflow[63]. The general technique in diffusion tensor imaging pipeline processing and analysis involves a few steps that include artifacts and data acquisition technique, quality control and pre-processing, processing and visualization, quantitative analysis; these can involve multimodal studies, and lastly, result interpretations. FA: Fractional Anisotropy; MD: Mean diffusivity; ROI: Region of interest; VBA: Voxel based analysis; TBSS: Tract based spatial statistics.

On the other hand, TBBS is a programmed technique for detecting group voxel-wise changes in the whole brain, established on the skeletonization of the group registered FA maps.

Whilst significant advancements over past two decades have been made in methodical technologies and breadth of applications, there remains no consensus on the ‘gold standard’ quantitative pipeline processing for CSVD studies – be it from diagnostic to prognostic implication. Most of the research teams used their own and different combinations in their pipelines[76,77] to assist with anatomical structures[75].
accuracy and interpreting results in research or clinical setting are done with caution. The four pipeline processing modalities described herein (Pipeline 1 to 4) are generally adopted in assessing white matter integrity in CSVD (as summarised in Figure 4).

**Pipeline 1**

Pipeline 1 (P1) consists of MRI Converter version 2.1.0, Brain Software Library or FSL Toolbox functional magnetic resonance imaging, and MedINRIA 2.2[70] as shown in Figure 4. MRI Convert is a medical image file conversion utility that can convert DICOM files to other formats including NIfTI format, FSL NIfTI format, analyze format, SPM99/Analyze format, Brain Voyager, and Metalmage volume formats. It creates a directory structure based on series and subjects. These directories and output files are given default names based on the subject, study, and series information and can be changed by the user.

FMRIB’s Diffusion Toolbox and BET-FSL are software tools for DWI analysis and are part of FMRIB’s Software Library (FSL) that can operate on Windows and Mac. It has a user-friendly graphical interface and command-line interface. It provides tools for data processing, local diffusion modelling, and tractography which work independently from each other. NIfTI Tools installed in MATLAB-Script is a tool that is used for motion and coordination correction or cleaning process. MedINRIA is an open-source software for medical image processing and visualization[78]. It offers database management and file import, 2D to 4D image visualization, diffusion image processing, segmentation of images, filtering of images and registration of images and has a strength in visualization aids.

The first step is the DICOM data of each participant is loaded into MRI Converter, converting the DICOM file format (.dcm) into NIfTI file format (.nii). Then, the DTI files are processed using the FSL toolbox that include eddy current correction (removal of artifact) and brain extraction tool (BET) (remove the skull and non-brain structure)[79]. The required data for eddy current correction is dti.nii, with corrected outputs being dti.data.nii.gz and dti.data.nii. It is assigned with such name to make further work easier. FSL toolbox is installed using a Virtual machine workstation that serves as a platform for Linux virtualization in Windows due to the incompatibility of the FSL toolbox to be installed directly to Windows. Then, the data from the FSL toolbox will undergo cleaning using NIfTI tools installed in MATLAB. Next, the clean DTI files are then uploaded on MedINRIA[70] to further the process of tensor estimation, whole brain, and ROI tractography analysis.

**Pipeline 2**

Pipeline 2 (P2) consists of MRIConverter version 2.1.0 and DSIStudio[71] software (http://dsi-studio.labsolver.org/). DSI Studio is a software for diffusion MRI analysis that provides functions including reconstruction, deterministic fiber tracking, and 3D visualization[70]. Additionally, DSI Studio can rotate to the source image to correct image orientation and present a real 3D tractography representation. DSI Studio’s fiber tracking algorithm is a simplified variant of the deterministic tracking algorithm that uses measurable anisotropy as the final indicator[71]. A deterministic method is used as the main axis of the tensor. The tensor aligns with the main direction of the fiber that follows the optimal path. Most likely to suggest fiber orientation for each voxel. This approach aims to find the best trade-off between valid and invalid connections[80].

The first step is to import the DICOM data of each participant into the MRI converter and converted the DICOM file format (.dcm) to the NIfTI file format (.nii). The initial stage is to mask the brain to remove non-brain structures and the skull (skull stripping). Eddy corrected DTI images with.nii/bvec/ bvec are primarily employed in this scenario. By default, all the settings are set to their default values. The data is then opened in DSI Studio, and the output of eddy corrected DTI generated a .src file. Next, the .src file is reconstructed, fib data is retrieved to track the fibers and tractography, and the FA value is then recorded.

**Pipeline 3**

Pipeline 3 (P3) consists of MRI Converter version 2.1.0, FSL toolbox, Diffusion toolkit, and TrackVIs[70]. DTI-Toolkit is a spatial normalization and atlas construction toolkit optimized to examine white matter morphometry using DTI data[81]. It supports a standard-based IO file such as NIfTI. Users may need to know simple Unix command lines to conduct certain tasks. It also provides a chain of tools to manipulate tensor image weight such as resampling, smoothing, warping, registration, and visualization. It is free software under public license and easily used but does not support tensor reconstruction (pre-processing support) and probabilistic fiber tractography. It applies tensor-based registration using explicit optimization of tensor reorientation analytically to give the best performance for fiber tract analysis compared to other tools[82].

TrackVIs is a complete software package that does reconstruction, fiber tracking, analysis, and visualization. It can not only handle diffusion tensor data but can also process high angular resolution diffusion imaging (HARDI) data as well as diffusion spectrum imaging data and Q-Ball imaging data. It is stand-alone, cross-platform (works on all major platforms, including Windows XP, Mac OS X, and Linux), fast and efficient. TrackVIs can read in the track data file and visualizes and analyses the tracks by user’s manipulation. TrackVIs can read entire brain track information typically more noteworthy.
Figure 4: Summarize processing for different pipeline processing. General methods for four pipelines processing that includes white matter hyperintensities detection and evaluation, pre-processing, processing, and post-processing. WMH: White Matter Hyperintensities; ROI: Region of interest; FA: Fractional anisotropy; MD: Mean diffusivity; AD: Axial diffusivity; RD: Radial diffusivity.

Pipeline 4

Pipeline 4 (P4) consists of MRI Converter version 2.1.0, and 3DSlicer. 3D slicer is a software platform for the analysis and visualization including volume rendering, registration, and interactive segmentation of medical images and research in image-guided therapy. It is free and open-source software that is extensible, with powerful plug-in capabilities for adding algorithms and applications. First is to load the DICOM data into the MRI Converter, converting the DICOM file format (.dcm) into the NIfTI file format (.nii). Next is to upload the data through data loading, and then the data is converted into nearly raw raster data (.nrrd). Thus, this data can be used freely in this 3D Slicer. From this data, open the DTI file in (.nrrd) format, and choose the slicer DMRI program in the menu bar to undergo diffusion and to attain the tensor data. From the tensor data, we can convert the data to tract by using the draw effect tool. Then, the tract is converted into tractography by using tractography seeding in the 3D Slicer program and the tractography is then generated with the DTI parameter value. Finally, the
same steps are repeated for ROI analysis in the 3D Slicer. Table 2 summarises the relevant previous studies (apart from CSVD) where software in these four pipelines is utilised in image computing for quantitative imaging networks [83-94].

### CLINICAL RELEVANCE OF PIPELINE PROCESSING

Taken together, DTI is a specialized diagnostic imaging tool utilizing diffusion-weighted imaging of MRI. Further studies and improvements of the DTI are warranted in advancing its utility in everyday patient care. As with any modality or imaging tool, deliberation with referring physicians, physician assistants, and nurse practitioners to increase awareness of this new option is clinically beneficial. Continuing research on its growing capabilities offer a wider adoption among health professional, especially among radiologists in interpreting the clinical merits of DTI. As radiologists see the value in DTI, more precise recommendations can be made to acquire DTI that can aid in diagnoses and/or prognoses of numerous other diseases.

### CONCLUSION

This short review highlights the potential role of DTI development and technology in our pursuit to understand the pathophysiology of CSVD. We summarise key aspects of DTI pipeline analysis and the clinical significance of pipeline processing that are pertinent for CSVD, in specific. As the interests in the field undoubtedly continue to grow, DTI metrics may serve as biomarker for routine clinical use to guide diagnosis, disease progress and prognosis for CSVD natural history, from it’s covert to symptomatic manifestations.

### ACKNOWLEDGEMENTS

We wish to thank the Director of the Universiti Hospital of Universiti Sains Malaysia for the permission to use numerous anonymised imaging datasets in our on-going related research on CSVD.

### FOOTNOTES

**Author contributions:** Ahmad Safri A, Nassir CMNCM and Muzaimi M contributed to writing–original draft preparation; Nassir CMNCM, Nurul Iman I, Mohd Taib NH, Achuthan A, and Muzaimi M contributed to writing–review and editing; all authors made substantial contribution to revising the manuscript critically for important intellectual content and approved the final manuscript.

**Conflict-of-interest statement:** All the authors declare that they have no conflict of interest.

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M. Aberrant Neurogliovascular Unit Dynamics in Cerebral Small Vessel Disease: A Rheological Clue to Vascular Resonance Imaging Associated With Stroke Symptoms in Small Vessel Disease?

Osman O

Wang Z

Disease.

Tensor Imaging Biomarkers for Cognitive Decline From the Preclinical Stage: A Study of Post-stroke Small Vessel Disease.

Lambert C

Liu JH

REFERENCES


23 Che Mohd Nassir CMN, Damodaran T, Yusof SR, Norazit A, Chilla G, Huen I, K N BP, Mohamed Ibrahim N, Mustapha M. Aberrant Neurogliovascular Unit Dynamics in Cerebral Small Vessel Disease: A Rheological Clue to Vascular...


Safri AA. DTI for cerebral white matter integrity


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8462

August 26, 2022

Volume 10

Issue 24
Graft choices for anterolateral ligament knee reconstruction surgery: Current concepts

Byron Chalidis, Charalampos Pitsilos, Dimitrios Kitridis, Panagiotis Givissis

Abstract
The anterolateral ligament (ALL) is a primary structure of the anterolateral complex of the knee that contributes to internal rotational stability of the joint. Injury of the ALL is commonly associated with rupture of the anterior cruciate ligament. If left untreated, ALL lesions may lead to residual anterolateral rotational instability of the knee after anterior cruciate ligament reconstruction, which is a common cause of anterior cruciate ligament graft failure. The function of the ALL can be restored by lateral extraarticular tenodesis or anterolateral ligament reconstruction (ALLR). In the lateral extraarticular tenodesis procedure, a strip of the iliotibial band is placed in a non-anatomical position to restrain the internal rotation of the tibia, while in ALLR, a free graft is fixed at the insertion points of the native ALL. Gracilis and semitendinosus grafts have mainly been utilized for ALLR, but other autografts have also been suggested. Furthermore, allografts and synthetic grafts have been applied to minimize donor-site morbidity and maximize the size and strength of the graft. Nevertheless, there has been no strong evidence to fully support one method over another thus far. The present review presents a detailed description of the graft choices for ALLR and the current literature available in regard to the effectiveness and outcomes of published surgical techniques.

Key Words: Anterolateral ligament; Reconstruction; Lateral extraarticular tenodesis; Anterior cruciate ligament; Hamstrings; Gracilis; Semitendinosus

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Core Tip: There is no convincing evidence regarding the biomechanical and functional superiority of either lateral extraarticular tenodesis or anterolateral ligament reconstruction procedures during anterior cruciate ligament reconstruction. Although hamstrings remain the most common graft choice for anterolateral ligament reconstruction, other autografts as well as allografts and synthetic grafts have been applied. Further research and comparative studies should be carried out to identify the most effective graft material and technique for the restoration of rotational knee stability in the presence of residual instability after anterior cruciate ligament reconstruction.

Citation: Chalidis B, Pitsilos C, Kitridis D, Givissis P. Graft choices for anterolateral ligament knee reconstruction surgery: Current concepts. World J Clin Cases 2022; 10(24): 8463-8473
URL: https://www.wjgnet.com/2307-8960/full/v10/i24/8463.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i24.8463

INTRODUCTION
The anterolateral ligament (ALL) is an independent structure of the anterolateral complex of the knee along with the lateral collateral ligament (LCL), the iliotibial band (ITB) and the anterolateral joint capsule[1,2]. There is no consensus so far on whether ALL bony attachment is located posterior and proximal or anterior and distal to the lateral femoral epicondyle or just on the lateral epicondylar together with the LCL attachment[3-7]. Its course is anterodistal and superficial to the LCL and its distal insertion midway between the anterior border of the fibular head and the Gerdy’s tubercle of the tibia [8]. The ALL is a nonisometric structure that tenses during knee flexion and internal tibial rotation and shows the greatest length change at 90° of flexion[9]. As a distinct structure of the anterolateral complex of the knee, the ALL seems to contribute to internal rotational stability of the joint, but its role in resisting rotational as well as anteroposterior instability in an anterior cruciate ligament (ACL) deficient knee is still controversial[10-13].

An ALL lesion is presented as a midsubstance strain and tear or avulsion of its bony insertion on the tibia, which is known as a Segond fracture[14]. The injury is most commonly associated with ACL rupture[5]. Concomitant ACL and ALL deficiency may result in increased knee rotational instability, which may not be restored by isolated anterior cruciate ligament reconstruction (ACLR)[15]. The incidence of positive pivot shift after ACLR could rise to 34% of operated cases, and many studies have demonstrated that additional ALL reconstruction (ALLR) decreases knee laxity and ACL graft failure rate and improves patient-reported outcomes[16-20]. On the other hand, simultaneous ALLR has been associated with overconstrained internal rotation and subsequent knee joint stiffness[21,22]. Furthermore, there is some evidence that ALLR does not decrease the rotational laxity of the knee to a desirable degree and its role in improving the postoperative function is limited[23,24]. Thus, simultaneous ACLR and ALLR have been suggested mainly in cases of grossly unstable pivot-shift and revision ACL surgery[25,26]. Moreover, indications for ALLR may include young patients who participate in pivoting activities as well as knees with chronic ACL deficiency or concomitant meniscal tears requiring surgical repair[27].

LITERATURE SEARCH
We conducted a narrative review using the MEDLINE online database regarding ALLR. The initial search applying the keywords “Anterolateral Ligament Reconstruction” led to 807 results. After abstract and full-text screening, 22 studies describing the results of ALLR in ACLR surgery were enrolled for further assessment (Figure 1). The extracted data were analyzed and organized to present the different reported methods of ALLR during ACLR in respect to graft choice, proximal and distal attachment location, stabilization technique and knee fixation angle (Table 1).

GRAFT TYPES AND TECHNIQUES
So far, many grafts have been applied for the restoration of ALL function, but no consensus exists regarding the ideal graft type and fixation technique. Controversies are based on the anatomic parameters of ALL regarding its bony origin and its length changes during knee motion. They are referred to graft material choice as well as graft insertion site location and fixation angle[6,8,23,28-33]. All the applied procedures aim to restore the knee kinematics in case of ALL deficiency and include either the lateral extraarticular tenodesis (LET) or ALLR techniques. The main principle of the LET
## Table 1 Graft choices and fixation methods

<table>
<thead>
<tr>
<th>Ref.</th>
<th>ACL graft type</th>
<th>ALL graft type</th>
<th>Femoral fixation point</th>
<th>Tibial fixation point</th>
<th>Fixation Technique</th>
<th>Knee flexion/rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemaire and Combelles [36], 1980</td>
<td>BTB (hole for ITB graft)</td>
<td>ITB</td>
<td>Above the lateral epicondyle, proximal to the LCL insertion</td>
<td>Maintain attachment to Gerdy’s tubercle</td>
<td>Two bone tunnel, suture on itself</td>
<td>30° flexion/external rotation</td>
</tr>
<tr>
<td>Andrews and Sanders [41], 1983</td>
<td>ITB (two strips)</td>
<td>Lateral femoral epicondyle</td>
<td>Maintain attachment to Gerdy’s tubercle</td>
<td>Suture strips together at medial femoral epicondyle after passing through two parallel lateral-to-medial tunnels</td>
<td>90° flexion/external rotation</td>
<td></td>
</tr>
<tr>
<td>Amirault et al [42], 1988</td>
<td>ITB</td>
<td>Above the lateral epicondyle, proximal to the LCL insertion</td>
<td>Maintain attachment to Gerdy’s tubercle</td>
<td>Suture fixation to ITB after passing through the lateral intermuscular septum</td>
<td>90° flexion/external rotation</td>
<td></td>
</tr>
<tr>
<td>Christel and Dijian [37], 2002</td>
<td>ITB</td>
<td>Above the lateral epicondyle, proximal to the LCL insertion</td>
<td>Maintain attachment to Gerdy’s tubercle</td>
<td>Interference screw</td>
<td>30° flexion</td>
<td></td>
</tr>
<tr>
<td>Mathew et al [38], 2018</td>
<td>ITB</td>
<td>Anterior and proximal to the lateral gastrocnemius tendon</td>
<td>Maintain attachment to Gerdy’s tubercle</td>
<td>Richards staple and sutures to itself</td>
<td>60° flexion/neutral rotation</td>
<td></td>
</tr>
<tr>
<td>Abusleme et al [39], 2021</td>
<td>ITB</td>
<td>Above the lateral epicondyle, proximal to the LCL insertion</td>
<td>Maintain attachment to Gerdy’s tubercle</td>
<td>Suture fixation to ITB after passing through the lateral intermuscular septum</td>
<td>90° flexion/neutral rotation</td>
<td></td>
</tr>
<tr>
<td>Colombet [49], 2010</td>
<td>Quadruple (Semitendinosus double-bundle and gracilis double-bundle) or Double (single-bundle each)</td>
<td>Gracilis - semitendinosus (one bundle each)</td>
<td>Proximal to lateral epicondyle</td>
<td>Gerdy’s tubercle</td>
<td>Absorbable screws at each fixation point</td>
<td>90° flexion/neutral rotation</td>
</tr>
<tr>
<td>Helito et al [29], 2015</td>
<td>Quadruple (semitendinosus triple-bundle and gracilis single-bundle)</td>
<td>Gracilis (single-bundle)</td>
<td>3-4 mm below the halfway point on the Blumensaat’s line in the AP direction</td>
<td>5-10 mm below the lateral tibial plateau, between fibular head and Gerdy’s tubercle</td>
<td>One 5 mm metal anchors at each fixation point</td>
<td>60-90° of flexion/mm</td>
</tr>
<tr>
<td>Smith et al [45], 2015</td>
<td>Semitendinosus graft</td>
<td>Gracilis (double-bundle)</td>
<td>Anterior to lateral femoral epicondyle</td>
<td>Midway between fibular head and the Gerdy’s tubercle, 11 mm distal to joint line</td>
<td>4.75 or 5.5 mm bioabsorbable knotless suture anchor at each fixation point</td>
<td>30° of flexion/neutral rotation</td>
</tr>
<tr>
<td>Ferreira et al [46], 2016</td>
<td>Semitendinosus triple-bundle</td>
<td>Gracilis (double-bundle)</td>
<td>8 mm posterolaterally from lateral epicondyle</td>
<td>9-13 mm distal to lateral joint line, between fibular head and the Gerdy’s tubercle</td>
<td>Interference screw 2 mm larger than tunnel</td>
<td>45-60° flexion/mm</td>
</tr>
<tr>
<td>Sonnery-Cottet et al [44], 2016</td>
<td>Semitendinosus SAMBBA</td>
<td>Gracilis (double-bundle)</td>
<td>Proximal and posterior to lateral epicondyle</td>
<td>One superolateral margin of the Gerdy’s tubercle and one midway between fibular head and the Gerdy’s tubercle</td>
<td>4.75 or 5.5 mm bioabsorbable knotless suture anchor at each fixation point</td>
<td>Full extension/neutral rotation</td>
</tr>
<tr>
<td>Delaloye et al [47], 2018</td>
<td>Internal brace</td>
<td>Gracilis (double-bundle)</td>
<td>Proximal and posterior to lateral epicondyle</td>
<td>Bone tunnel: One point just anterior to the fibular head and second posterior to Gerdy’s tubercle</td>
<td>4.75 bioabsorbable knotless suture anchor at femoral fixation point</td>
<td>Full extension/neutral rotation</td>
</tr>
<tr>
<td>Saithna et al [18], 2018</td>
<td>Quadruple (Semitendinosus triple-bundle and gracilis single-bundle)</td>
<td>Gracilis (single-bundle)</td>
<td>Proximal and posterior to lateral epicondyle</td>
<td>Bone tunnel: One point just anterior to the fibular head and second posterior to Gerdy’s tubercle</td>
<td>Ethibond suture around the graft</td>
<td>Full extension/neutral rotation</td>
</tr>
<tr>
<td>Goncharov et al [46], 2019</td>
<td>BTB autograft</td>
<td>Gracilis or semitendinosus tendon autograft</td>
<td>Proximal to lateral epicondyle</td>
<td>10 mm distal to joint line, between fibular head and the Gerdy’s tubercle</td>
<td>Interference screws</td>
<td>Full extension/mm</td>
</tr>
</tbody>
</table>
procedure is the use of a strip of ITB that is stabilized proximally above the knee joint while its tibial insertion to Gerdy’s tubercle remains intact[34]. On the other hand, the ALLR aims to restore the ALL native features by fixing a free tendon graft between the anatomical femoral and tibial insertion points of the ALL[35].
**AUTOGRAFTS**

**Iliotibial band**
The ITB is exclusively used for the LET procedure. Lemaire[36] was the first who described the LET technique in cases of chronic ACL injuries. In the original procedure, the ITB was identified and a strip of 1 cm wide and 18 cm long was harvested, leaving the attachment to Gerdy’s tubercle intact. The graft was first passed in a distal to proximal direction under the LCL. Then, it was introduced to the distal femur through a bone tunnel above the lateral epicondyle and proximal to the LCL insertion. Consequently, it was passed again under the LCL in a proximal to distal direction and finally fixed to the tibia through a bone tunnel at Gerdy’s tubercle and sutured on itself. Fixation was completed in 30° of knee flexion and some tibial external rotation. In cases of combination with ACLR, LET allows for independent ACL graft choice. The authors also proposed a variation of the original technique by fixing the strip of ITB into the femoral tunnel that was created for bone-patellar tendon-bone graft ACLR.

Many modifications of the Lemaire procedure have been described referring to harvesting a shorter strip of tendon[37,38]. In addition, the graft may be stabilized proximally with sutures to the ITB after passing through the lateral intermuscular septum or with either a staple or an interference screw[37-40]. Andrews and Sanders[41] described a technique where two strips of ITB were harvested and passed through two parallel lateral-to-medial femoral tunnels and sutured together.

Moreover, variable knee flexion angles have been recommended during fixation, including 30°, 60° and 90°[38,39,42]. In respect to tibial rotation, older studies suggested that the tibia should be maintained in external rotation, but no specific angle was defined[40,41]. However, that position has been related to excessive restriction of internally rotatory movement and abnormal knee kinematics[34,43]. This overconstraining along with the non-anatomic nature of the LET procedure may lead to gradual elongation of the graft and subsequent recurrent rotational instability[43]. As a result, most recent studies have advocated a neutral rotation position for ITB graft fixation[38,39].

**Gracilis tendon**
Gracilis tendon (GT) is a commonly used autograft for ALLR. The free tendon graft is fixed proximally on the lateral femoral epicondyle and distally between the fibular head and Gerdy’s tubercle after passing between the ITB and LCL[19]. Most frequently, the graft is introduced proximal and posterior to the lateral femoral, but a more anterior position has also been described[44,45]. Femoral fixation can be performed with an interference screw or an anchor[45,46]. The same principles are followed when concomitant ACLR is performed with either hamstrings graft, bone-patellar tendon-bone graft or internal brace[44-47].

The tibial attachment of the graft is placed between the fibular head and Gerdy’s tubercle approximately 5 to 13 cm distal to the lateral joint line[29,48]. Fixation is accomplished using an interference screw or an anchor[29,49]. Some authors have described ALLR in an inverted V-shaped fashion. Specifically, the graft is introduced in a tibial bone tunnel extending anterior to the fibular head and posterior to Gerdy’s tubercle and then is fixed at the femoral side with an anchor or with sutures around the graft[18,47]. Sonnery-Cottet et al[44] completed tibial fixation of the graft with two suture anchors. The first one was placed on the superolateral margin of the Gerdy’s tubercle and the other one midway between the fibular head and Gerdy’s tubercle.

During combined ALLR and ACLR using hamstring tendon autograft, a single graft is usually used for both procedures. After ACLR, the remaining graft is passed through a bone tunnel to the lateral surface of the distal femur, proximally and posteriorly to the lateral epicondyle[18,48]. Helito et al[29] identified the ALLR femoral tunnel location using fluoroscopy, aiming approximately 3-4 mm below the halfway point of the Blumensaat’s line in the anteroposterior direction. Furthermore, Ferreira et al[48] used a triple semitendinosus tendon (ST) graft for ACLR and a double GT graft for ALLR. Another combination is a four-strand ACL graft formed by a triple ST bundle and a single GT bundle, while the remaining GT is used for ALLR[29]. Colombet[49] also described the use of a quadruple ACL graft composed of two ST and two GT bundles. A double-bundle graft for ALLR was created from the excess tendon tissue of the bundles.

There is no consensus regarding the ideal fixation angle of a GT graft. Several different knee angles have been reported so far including full extension, 30°, 45° to 60°, 60° to 90° and 90°[29,45,47-49]. In contrast, it has been generally accepted that the tibia should be maintained in neutral rotation at the time of graft stabilization[18,44,45].

**Semitendinosus tendon**
Apart from GT, the ST has been also widely used for ALLR[46]. Kim et al[50] harvested the contralateral ST for ALLR, as the ipsilateral ST had been already used for ACLR during the same or previous procedure. The double-bundle graft was first attached on the tibia (midway between the fibular head and Gerdy’s tubercle) using an adjustable length loop button, then passed deep to ITB and finally fixed posterior and proximal to the lateral femoral epicondyle with an interference screw, while the knee was positioned in 30° of flexion and neutral rotation. Additionally, Zarins and Rowe[51] proposed simultaneous ACLR and ALLR using only the ipsilateral ST. After proximal release, the ST was passed...
through the knee joint for ACLR, then exerted through a lateral femoral bone tunnel and tied to the ITB keeping the knee in 60° of flexion and tibial external rotation.

**Peroneus longus**

Escudeiro de Oliveira *et al* [52] reconstructed the ALL with an ipsilateral peroneus longus (PL) tendon graft and the ACL with a quintuple graft composed of a double-bundle ST, a double-bundle GT and a single-bundle PL. Specifically, the quintuple graft was initially used for ACLR, and the excess PL material was passed through a femoral tunnel, proximal and posterior to the lateral epicondyle, and was attached distally between the fibular head and Gerdy’s tubercle at 15 mm from the joint line. An interference screw was used in each attachment site, and during fixation the knee was kept at mild valgus and 30° of flexion. The authors supported the option of PL graft for ALLR as it could be easily harvested with minimal invasiveness. It was associated with low donor site morbidity and allowed adequate concomitant ACLR in combination with hamstring tendon autograft.

**Plantaris longus**

Josipovic *et al* [53] presented a technique of ALLR using the ipsilateral plantaris longus tendon. A quintuple graft composed of a three-strand ST and a two-strand GT was used for ACLR and a two-strand plantaris longus graft, which substituted the ALL, sutured to the quintuple graft. After the ACL graft fixation, the plantaris longus tendon was passed through a bone tunnel posterior and proximal to the lateral femoral epicondyle and fixed with an interference screw 10 mm distally from the joint line and midway between the fibular head and Gerdy’s tubercle, while the knee was fully extended. Although the authors reported good short-term results, there was a lack of data regarding the effectiveness of the technique.

**Quadriceps and patellar tendon grafts**

Historically, Marshall *et al* [54] presented the Marshall-MacIntosh procedure using an autograft of quadriceps tendon-prepatellar retinaculum-patellar tendon for concomitant ACL and ALL reconstruction. The distal attachment of the extensor apparatus to the tibial tubercle was preserved, and the graft was passed through a tibial and femoral bone tunnel over the top of the lateral femoral condyle and fixed on Gerdy’s tubercle. Dupont *et al* [55] presented a modification of the technique by harvesting a free graft including the bony attachment of the quadriceps tendon-prepatellar retinaculum-patellar tendon on the tibial tubercle. Additionally, Benum [42] reported the use of the lateral one-third of the patellar tendon with a proximal bone block for ALLR. The distal attachment on the tibial tubercle was preserved, and the graft was fixed with staples to the femoral origin of LCL.

**ALLOGRAFTS**

Some authors have recommended the application of allografts for ALLR, even in primary surgery, emphasizing the advantages of no donor site morbidity and availability of larger and longer grafts [56]. However, the use of allografts has been mainly suggested in revision surgery, where autografts may be not available in sufficient quantity [57]. Lee *et al* [25] used a GT allograft for ALLR in combination with tibialis anterior allograft for ACLR in the setting of revision surgery. Comparing ACLR with and without ALLR, they reported better outcomes after at least 3 years in terms of residual pivot shift, subjective IKDC score and Tegner score, return to the preinjury level of sports activity and possibility of revision surgery when ALLR was additionally performed. Chahla *et al* [57] underwent ALLR using an ST allograft mainly in cases requiring revision ACL surgery. However, they did not present any postoperative outcomes. Fernández *et al* [58] used an Achilles tendon allograft for both ACLR and ALLR in patients with previously failed ACLR and significant bone loss. They performed a two-stage procedure to fill the bone defect with a bone graft and to subsequently reconstruct the ACL and ALL. Still, no postsurgical outcome was reported.

**SYNTHETIC GRAFTS (POLYESTER TAPE)**

Wagih and Elguindy [59] reported an ALLR technique using polyester tape. The synthetic ligament was attached proximally anterior and distal to the lateral femoral condyle with a cortical suspensory button. Distally, the graft was inserted between the Gerdy’s tubercle and the fibular head and stabilized via sutures that tied on the medial side of the tibia through two bone tunnels. During fixation, the knee was placed in 30° of flexion. The authors suggested that polyester tape ALLR might be worth further investigation as it was a minimally invasive technique without donor site morbidity. Furthermore, the material could offer adequate strength with minimal possibility of laxity and postoperative failure. However, no details about the postoperative outcome were provided.
BIOMECHANICAL EVALUATION

The combination of ACLR with LET or ALLR can restore residual rotational laxity after isolated ACLR [60]. However, the LET procedure has been related to postoperative overconstraint of the internal rotation of the knee [34]. In a cadaveric study, Smith et al. [34] reported similar results and equivalent restoration of knee kinematics between ALLR and LET and after ACLR. Regarding knee position during graft fixation, Inderhaug et al. [61] in a controlled ACLR laboratory study found that knee laxity was equally restored when ITB graft tenodesis was performed at 0°, 30° or 60° of knee flexion. On the other hand, ALLR using a GT graft achieved normal kinematics only when fixation was performed in full extension. Conversely, in another cadaveric study, Geeslin et al. [62] found that both LET and ALLR were effective in reducing internal tibial rotation independently of the knee fixation angle or graft tension.

Additionally, Monaco et al. [63] noticed that ALLR with GT showed superior biomechanical properties than LET, while the native ACL had lower failure load and stiffness compared to both grafts. Ra et al. [64] found that LET resulted in similar rotational stability but worse anterior instability compared to ALLR. On the contrary, Spencer et al. [65] reported that ALLR was less effective in reducing anterolateral rotational laxity than the LET procedure. Deviandri and van der Veen [66] used LET in four patients with residual rotational instability after ACLR and reported a significant improvement of knee kinematics.

In a recent meta-analysis, Yin et al. [67] reported superior knee kinematics after combined ACLR and ALLR or LET compared to isolated ACLR in ACL deficient knees. Similarly, Littlefield et al. [69] in a systematic review identified that supplementary ALLR during ACLR improved anterior tibial translation and internal knee rotation and resulted in a lower incidence of graft failure.

CLINICAL EVIDENCE

Current literature suggests that combined ACLR with ALLR or LET can improve clinical outcomes and decrease the possibility of ACL graft failure compared to isolated ACLR [43]. Beckers et al. [68] observed that both LET and ALLR during ACLR provided superior Lysholm Score and reduced ACL re-rupture rate. Na et al. [69] in a systematic review found that ALLR or LET along with ACLR were related to superior subjective IKDC, Tegner and Lysholm scores than isolated ACLR. However, the LET was associated with higher postoperative stiffness and complications than ALLR. Sonnery-Cottet et al. [70] using data from 270 patients noticed that combined ACLR with ALLR led to a lower reoperation rate and better long-term graft survivorship but similar overall complication risk compared to isolated ACLR. The authors reported a 5-fold increase in the risk of ACL graft failure after a mean of 104 mo in cases of isolated ACLR. Similarly, in a systematic review of de Lima et al. [71] the simultaneous ALLR and ACLR were related to better clinical outcomes than single ACLR, including higher success in return to sport and lower ACL graft rupture rate. The advantages and disadvantages of each technique are summarized in Table 2.

DISCUSSION

Restoration of rotational stability is of paramount importance in the ACL injured knee. Apart from intraarticular ACLR, additional extraarticular procedures may be required to improve knee function and stability and minimize the risk for ACL graft failure. These include the LET and the ALLR with variable modifications of each procedure regarding the graft choice and fixation technique. Semitendinosus and gracilis are the main tendon grafts for ALLR, but other autografts such as peroneus longus, plantaris longus and quadriceps-patellar tendons have also been applied. Allografts and synthetic grafts are usually preferred in revision ACLR procedures where there is limited availability of autograft material for both ACLR and ALLR. Although all the available grafts for LET and ALLR may improve knee rotational stability, few studies with a relatively short follow-up and a small number of patients have been published so far. Therefore, there is inconclusive evidence to favor one method over the others in terms of biomechanical properties and clinical outcomes. Further large-scale studies are required to clarify the benefit of ALLR during primary or revision ACLR procedures. Particularly, future randomized control trials should compare ACLR with or without ALLR in young, active and high-demand patients by using different graft types. The research should focus on the subgroup of patients with large pivot-shift and operated meniscal tears aiming to find a potential correlation between ALLR and failure of ACLR under these conditions.

CONCLUSION

According to the current review and existing literature, there is no convincing evidence regarding the
### Table 2 Lateral extraarticular tenodesis and anterolateral ligament reconstruction Techniques: Advantages and disadvantages[39,72,73]

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lateral extraarticular tenodesis</td>
<td></td>
</tr>
<tr>
<td>Improvement of rotational knee stability</td>
<td>Non-anatomic procedure</td>
</tr>
<tr>
<td>Reduction of ACL graft failure rate</td>
<td>Possible over-constraining</td>
</tr>
<tr>
<td>Reproducible, easy-to-learn technique</td>
<td>May add pain to postoperative rehabilitation</td>
</tr>
<tr>
<td>Inexpensive procedure, especially when using high-resistance suture</td>
<td>Muscle herniation, if ITB closure is not performed in proper way</td>
</tr>
<tr>
<td>No risk of tunnel coalition when fixed with sutures proximally</td>
<td></td>
</tr>
<tr>
<td>2. Anterolateral ligament reconstruction</td>
<td></td>
</tr>
<tr>
<td>Improvement of rotational knee stability</td>
<td>Need ability to identify anatomic landmarks</td>
</tr>
<tr>
<td>Reduction of ACL graft failure rate</td>
<td>Use of allograft or synthetic results in increased cost</td>
</tr>
<tr>
<td>Preserves iliotibial band</td>
<td>Use of autograft requires additional surgery for graft harvest and possible donor site morbidity</td>
</tr>
<tr>
<td>Avoids lateral collateral ligament attachment</td>
<td></td>
</tr>
<tr>
<td>Secure graft fixation allows for early motion and accelerated anterior cruciate ligament rehabilitation</td>
<td></td>
</tr>
</tbody>
</table>

ACL: Anterior cruciate ligament; ITB: Iliotibial band.

Biomechanical and functional superiority of either LET or ALLR procedures during ACLR. Although hamstrings remain the most common graft choice for ALLR, other autografts as well as allografts and synthetic grafts have been applied with satisfactory results and low complication rate. However, a pooled analysis of all published raw data would further improve the quality of the review and related evidence despite the heterogeneity of the studies.

**FOOTNOTES**

**Author contributions:** Chalidis B and Kitridis D designed the research; Pitsilos C analyzed the data; Chalidis B and Pitsilos C wrote the paper; Givissis P supervised the paper; All authors read and approved the final manuscript.

**Conflict-of-interest statement:** There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

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**S-Editor:** Wang LL

**L-Editor:** Filipodia

**P-Editor:** Wang LL

**REFERENCES**


Chalidis B et al. Review of ALLR grafts


Overview of the anterolateral complex of the knee

Ignacio Garcia-Mansilla, Juan Pablo Zicaro, Ezequiel Fernando Martinez, Juan Astoul, Carlos Yacuzzi, Matias Costa-Paz

Abstract

In the last few years, much more information on the anterolateral complex of the knee has become available. It has now been demonstrated how it works in conjunction with the anterior cruciate ligament (ACL) controlling anterolateral rotatory laxity. Biomechanical studies have shown that the anterolateral complex (ALC) has a role as a secondary stabilizer to the ACL in opposing anterior tibial translation and internal tibial rotation. It is of utmost importance that surgeons comprehend the intricate anatomy of the entire anterolateral aspect of the knee. Although most studies have only focused on the anterolateral ligament (ALL), the ALC of the knee consists of a functional unit formed by the layers of the iliotibial band combined with the anterolateral joint capsule. Considerable interest has also been given to imaging evaluation using magnetic resonance and several studies have targeted the evaluation of the ALC in the setting of ACL injury. Results are inconsistent with a lack of association between magnetic resonance imaging evidence of injury and clinical findings. Isolated ACL reconstruction may not always reestablish knee rotatory stability in patients with associated ALC injury. In such cases, additional procedures, such as anterolateral reconstruction or lateral tenodesis, may be indicated. There are several techniques available for ALL reconstruction. Graft options include the iliotibial band, gracilis or semitendinosus tendon autograft, or allograft.

Key Words: Anterolateral complex; Knee instability; Anterolateral ligament; Anterior cruciate ligament reconstruction

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Core Tip: Although research on anterolateral ligament (ALL) has increased considerably in recent years, some debate remains regarding its anatomy and further refinement is still ongoing. Biomechanical studies have revealed that anterolateral structures contribute significantly to rotational stability of the knee and should be accounted for in the setting of an anterior cruciate ligament (ACL) injury. Surgical indications for ALL reconstruction are not currently evidence-based and the ideal graft type and fixation have not yet been determined. Further clinical research remains to be conducted to determine the most appropriate scenarios for augmentation of a primary ACL reconstruction with an anterolateral procedure to enhance patient outcomes.

URL: https://www.wjgnet.com/2307-8960/full/v10/i24/8474.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i24.8474

INTRODUCTION

The initial description of the anterolateral complex of the knee is attributed to various authors, and the anatomical details of the so-called anterolateral ligament of the knee have changed according to the historical context of each century. In 1752, Weitbrecht was the first to refer to a series of fibers that reinforced the lateral joint capsule of the knee and that, according to his observation, gave support to the external meniscus. One hundred years later, Henle described a group of fibers anterior to the external collateral ligament that inserted into the edge of the external meniscus, and that reinforced the joint capsule. The first anatomico-clinical approach was advanced by Paul Segond who described an avulsion fracture of the anterolateral portion of the proximal tibia associated with this ligament. Through a series of cadaveric dissections, he characterized the fibers of the ligament as a stringy, beaded, tough band that, according to his observation, tightened upon excessive internal rotation of the knee. Since then, the ligament has taken different names in the literature and numerous and non-specific descriptions have been made of the ligamentous capsule structures of the anterolateral region of the knee\(^1_2\).

More than a century had to pass until the landmark works of Claes at al\(^3\), Vincent et al\(^4\) and Helito et al\(^5\) when the term anterolateral ligament of the knee began to spread. From that time on, there has been a great deal of dispute surrounding the presence of the LLA and its possible role in the control of anterolateral rotational instability (ALRI) following anterior cruciate ligament (ACL) injury. Great emphasis has been given to a better understanding of these structures, including their anatomy, biomechanics, injury patterns, and the optimal strategies to treat any rotational laxity of the knee resulting from damage to these structures\(^6\). Lateral extra-articular tenodesis has re-emerged in popularity and several ALL reconstruction techniques have been developed in the attempt to lower the failure rate following ACL reconstruction\(^7\-9\). The aim of this review is to outline the latest literature findings on the anatomy of the anterolateral complex, biomechanical findings, treatment of anterolateral lesions, and ALL reconstruction techniques. It is intended to provide information to readers on the most current approaches to help enhance patient outcomes following an ACL injury and subsequent reconstruction.

ANATOMY OF THE ANTEROLATERAL COMPLEX

The complex ligamentous capsule anatomy of the anterolateral region of the knee is given by the relative and multiplanar position adopted by its bony parts. To distinguish the anatomy of the anterolateral ligament, it is necessary to understand the three-dimensional arrangement of the iliotibial band. In this anatomical complex, which has been widely described, the following layers can be recognized: Superficial layer of the reflected iliotibial band (sITB) (Figure 1A): It is found immediately deep to the subcutaneous cellular tissue and superficial to the vastus lateralis, easily identifiable by its pearly white color. Its main insertion on Gerdy’s tubercle is distinguished distally. Its most anterior fibers are curved distally and insert on the lateral surface of the patella and the patellar tendon (iliopatellar band). Middle layer of the ITB (mITB): Made up of the patellofemoral ligament and the fascia of the quadriceps femoris. Its fibers, contrary to the vertical arrangement of the first layer, run obliquely from proximal and lateral to distal and medial. Deep layer of the ITB (dITB) (Figure 1B): It is localized posterior to the superficial layer. It is inserted into the distal femur, from its metaphyseal portion to the supracondylar area through the so-called Kaplan fibers. These fibers arrange transversely to the femur, which form the deep layer of the iliotibial band and, together with the superficial portion, have an important role in knee stability.
The anterolateral complex of the knee

The Capsulo-osseous Layer of the ITB and the anterolateral capsule. There is still considerable controversy surrounding the terminology of the joint capsule that underlies the deepest layer of the ITB. Some authors proposed a capsular-osseous layer and described it as a medial retaining wall of the deepest layer of the ITB. Distally, the fibers run just proximal to Gerdy’s tubercle, inserting posterior to the convergence between the superficial and deep layers of the iliotibial band. The lateral joint capsule comprises a superficial layer and a deep layer, based on their relation with respect to the lateral collateral ligament (LCL). Hughston et al. divided the deep capsule into three parts: an anterior layer (of minor importance due to its thickness and negligible insertions), a posterior layer (made up of the posterolateral arcuate complex) and an intermediate layer called the “mid-third lateral capsular ligament” (a capsular thickening with distinct femoral and tibial bony insertions). The latter also has a firm attachment to the lateral meniscus. These fibers form the meniscofemoral and meniscotibial ligaments, also known as the coronary ligament.

All these descriptions overlap with those of the anterolateral ligament of the knee, and can be understood as the same structure. In relation to its arrangement, its direction is from proximal and posterior to distal and anterior, inserted at the lateral epicondyle of the femur and the lateral articular margin of the external tibial condyle (Figure 1C). It is related to the lateral meniscus through the coronary ligament (Figure 1D). The proximal attachment is subject to debate, although most authors agree that it is located proximal and posterior to the center of the lateral femoral epicondyle.

IMAGING OF THE ANTEROLATERAL COMPLEX

X-radiographs

During the pivot shift phenomenon, internal rotation and anterior translation are responsible for the rupture of the ACL and for the load on other soft tissue structures attached to the lateral tibia, which will eventually could tear or avulse the lateral margin of the tibia (Segond fracture). There have been several studies that pointed out that the Segond fracture is caused by some capsule-ligamentous structure throughout the lateral aspect of the knee connecting the distal femur to the tibia.
Ultrasound
Visualization of the ALL on ultrasonography is challenging. Some studies showed that this structure could be identified at least partially on ultrasound. The sensitivity of this method varied, among different authors, between 60% to 100%[18,19]. However, it was not easy to isolate the ALL from the adjacent structures like the anterolateral capsule and the iliotibial band (ITB). Performing the ultrasound examination with the knee in internal rotation and flexion may improve the visualization of this ligament structure[20]. Even though anterolateral ligament injuries can be diagnosed with ultrasound, this imaging method is not routinely utilized in the diagnostic algorithm of these patients.

Magnetic resonance imaging
Many authors studied how to identify the ALL by magnetic resonance imaging (MRI), most of them agreed that this structure is difficult to analyze along its entire length and that is best identified in the coronal plane[21]. Clear identification of the ligament is described in more than half of the cases, varying between 51% and 100% in most studies. However, other authors visualized the ligament in only 11% of the cases[22-24]. The femoral origin is difficult to visualize because it is not clearly distinguishable from the LCL and ITB[25]. In injured knees, soft tissue swelling and joint effusion can provide signal intensification that may allow enhanced visualization of the ALL[21,23]. The true utility of MRI is its capacity to identify involvement of the ALL following knee injuries to potentially guide in deciding ligament reconstruction alternatives. Abnormal ALL includes one or the combination of the following features: complete disruption, irregular contour and ligamentous edema. This findings can correlate with an increase in pivot shift test[26].

BIOMECHANICAL FINDINGS
A developing body of literature has examined the role of anterolateral structures in rotatory knee stability. Given the high complexity of this region of the knee, with its varying anatomical structures, biomechanical studies have shown uncertain results. In a controlled laboratory study, Zens et al.[27] described the biomechanical properties of the ALL and found that the LLA becomes longer under flexion and internal rotation, while it becomes shorter under external rotation. The mean length change during internal rotation was also higher when the knee was flexed[27]. According to different studies, mean ultimate failure load ranged between 50 and 205 N, mean stiffness 20 to 42 N/mm, and mean ultimate strain 36%[27-29]. Sectioning of the ALL resulted in a statistically significant increase in anterior translation and internal knee rotation after ACL section[30-32]. However, a number of authors suggested that the ALL or anterolateral capsule plays just a minor role at physiologic ranges of tibial translation acting as a secondary stabilizer to anterolateral translation only after loss of the ACL[33-35]. Most biomechanical studies evaluated the anterolateral structures with preserved ITB. On the contrary, Kittl et al.[26] showed that when Kaplan’s fibers and the capsulo-osseous layer are disrupted, thus interrupting the functional unity of the ITB between the distal femur and the proximal tibia, the internal rotation of the tibia is substantially increased throughout range of motion[36]. Demonstrating a crucial contribution of the ITB to rotatory knee stability. In another study, Noyes et al.[35] observed that sectioning of the ALL and the ITB in ACL-deficient knees converted 71% of the specimens to a grade 3 pivot shift as measured by composite tibiofemoral translations and rotations. These results emphasize the importance of approaching the anterolateral complex of the knee as a unit rather than the antero-lateral ligament in isolation.

MANAGEMENT OF ANTEROLATERAL INJURIES
There is no agreement on the optimal treatment management strategy for anterolateral knee injuries and the possible long-term clinical impact of ALL insufficiency is currently unknown. As noted above, anterolateral structures contribute significantly to rotational knee stability and should be acknowledged in the setting of ACL reconstruction or revision surgery. Concomitant ACLR and ALL reconstruction (ALLR) significantly decreased internal rotation and tibial translation in the axial plane with respect to isolated ACLR in the presence of ALL deficiency[32]. The indication for lateral tenodesis or reconstruction procedures combined with ACL reconstruction is not clearly established in the literature and is typically based on surgeon’s experience and judgment[13,37]. Based on the risk factors for graft failure and the indications suggested in the available evidence, Table 1 shows a list of 14-criteria divided into major and minor criteria to be consider when evaluating the need for performing a lateral tenodesis or ALL reconstruction procedures. Considerable clinical research has yet to be accomplished to identify the best-case scenarios for augmentation of a primary ACL reconstruction with an anterolateral procedure to maximize patient outcomes.
### Table 1 List of 14-criteria divided into major and minor criteria to be considered when evaluating the need for performing a lateral tenodesis or anterolateral ligament reconstruction procedures

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACL revision; pivot shift grade III; pivot sports; competitive athlete or “elite”; age ≤ 25 yr old</td>
<td>Hyperlaxity/ recurvatum ≥ 10°; KT-1000 ≥ 8 mm side-side difference; instability ≥ 6 mo; medial meniscectomy and/or lateral meniscus root lesion; contralateral knee instability; BMI ≥ 30; tibial plateau slope ≥ 10°; severe anterior tibial translation; presence of a “lateral femoral notch sign” or an impaction of the lateral femoral condyle[39]; Segond fracture</td>
</tr>
</tbody>
</table>

ACL: Anterior cruciate ligament; BMI: Body mass index.

### Table 2 Anterolateral ligament reconstruction techniques

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Graft</th>
<th>Direction</th>
<th>Fixation site</th>
<th>Fixation angle</th>
<th>Graft fixation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grassi et al [43]</td>
<td>ITB</td>
<td>Deep to the LCL</td>
<td>Proximal and posterior to the lateral femoral condyle</td>
<td>Neutral rotation/0°-90°</td>
<td>Interference screw</td>
</tr>
<tr>
<td>Mahmoud et al [47]</td>
<td>ITB</td>
<td>Deep to the LCL and then passed through the lateral distal intermuscular septum from posterior to anterior and adjacent to the femur</td>
<td>Neutral rotation/around 30° flexion</td>
<td>ITB is sutured to itself at physiological tension</td>
<td></td>
</tr>
<tr>
<td>Arnold et al [48]</td>
<td>ITB</td>
<td>Under the LCL and the Popliteus tendon</td>
<td>External rotation/90°-100°</td>
<td>Sutured with periosteal stitches to GT</td>
<td></td>
</tr>
<tr>
<td>Porter et al [49]</td>
<td>ITB</td>
<td>Around the proximal LCL</td>
<td>Posterior to the Gerdy tubercle</td>
<td>Neutral rotation/35°</td>
<td>Interference screw</td>
</tr>
<tr>
<td>Losee et al [50]</td>
<td>ITB</td>
<td>Deep to the LCL</td>
<td>The femoral tunnel originated at the attachment point of the lateral gastrocnemius and ended antero-distal to the LCL femoral insertion site</td>
<td>External rotation/30°</td>
<td>Sutured at the Gerdy tubercle</td>
</tr>
<tr>
<td>Dejour et al [42]</td>
<td>ITB</td>
<td>Over the LCL</td>
<td>Anterior to the junction of the femoral shaft and lateral femoral condyle</td>
<td>External rotation/30°</td>
<td>1 Cancellous screws</td>
</tr>
<tr>
<td>Ellison et al [51]</td>
<td>ITB</td>
<td>Deep to the LCL</td>
<td>Slightly anterior to its original harvest site at the Gerdy tubercle</td>
<td>External rotation/90°</td>
<td>Interference screw</td>
</tr>
<tr>
<td>Lee et al [52]</td>
<td>Allograft</td>
<td>Over the LCL</td>
<td>Femur: Proximal and posterior to the lateral femoral condyle/Tibia: Between the fibular head and Gerdy tubercle at approximately 10 mm below the joint line</td>
<td>Neutral rotation/30°</td>
<td>2 Interferences screws³</td>
</tr>
<tr>
<td>Sonnery-Cottet et al [41]</td>
<td>Gracillis (ACL and ALL)</td>
<td>Single femoral tunnel/graft is routed deep to the iliotibial band from the femur to the tibia, shuttled through a tibial bony tunnel and back proximally to the femur</td>
<td>Proximal and posterior to the lateral femoral condyle</td>
<td>Neutral rotation/extension</td>
<td>Fixed to the ACL graft</td>
</tr>
<tr>
<td>Dejour et al [42]</td>
<td>Double hamstrings (ACL and ALL)</td>
<td>Over-the-top</td>
<td>Proximal and posterior to the lateral femoral condyle</td>
<td>90</td>
<td>Stapples</td>
</tr>
</tbody>
</table>

ITB: Reflected iliotibial band; LCL: Lateral collateral ligament; GT: Gerdy’s tubercle; ACL: Anterior cruciate ligament; ALL: Anterolateral ligament.

### SURGICAL TECHNIQUES

Several techniques have been described to perform an ALLR. The main goal is to control internal rotation and restore the normal knee kinematics. From a technical point of view, there are two surgical alternatives: a lateral extra-articular tenodesis (LET) or an "anatomical" reconstruction of the ALL. Different fixation sites, grafts, and fixation angles have been described (Table 2). Available evidence is based on mixed clinical and in vitro studies. No study has demonstrated improvement in subjective or objective outcomes of one procedure over the others[38]. Three recent systematic reviews with meta-analyses including only comparative studies have shown that the addition of a lateral extra-articular tenodesis procedure to an ACL reconstruction has been found to reduce rotational laxity control, but has no effect on anterior translation or patient-reported outcomes[9,39,40]. For the LET the most frequently used graft is the ITB and for the anatomical reconstruction the gracilis tendon or allograft.
The most frequent femoral insertion site is posterior and proximal to the lateral epicondyle. The ITB can be passed under or over the LCL. It can also be fixed anterior and distal to the epicondyle. Suture anchors, interference screws or cortical buttons can be used for graft fixation. Whichever technique is used, the most important consideration is to avoid the confluence of the tunnels with the ACL. This can usually be avoided easily by aiming the drill 30° proximal and 30° anterior. It is recommended to perform this step while directly visualizing the intra-articular femoral tunnel; positioning the arthroscope in the tunnel to confirm if necessary. Other techniques describe a mixture of intra-articular and extra-articular ACL reconstruction utilizing a unique graft through a single femoral tunnel as described by Sonnery-Cottet et al[41] or passing the graft over-the-top as described by Dejour et al[42], Grassi et al[43], Sarraj et al[44], Placella et al[45].

**CONCLUSION**

The findings outlined in the present mini-review contribute to the comprehension of the role of the anterolateral complex of the knee. Although research on ALL has increased considerably in recent years, some debate remains regarding its anatomy and further refinement is still ongoing. Biomechanical studies have revealed that anterolateral structures contribute significantly to rotational stability of the knee and should be accounted for in the setting of an ACL injury, especially in cases with a high degree of pivot shift or revision surgery. Surgical indications for ALL reconstruction are not currently evidence-based and the ideal graft type, fixation location and fixation angle have not yet been determined. Further clinical research remains to be conducted to identify the most appropriate situations for augmentation of a primary ACL reconstruction with an anterolateral procedure to enhance patient outcomes.

**FOOTNOTES**

**Author contributions:** Garcia-Mansilla I designed the study and drafted the manuscript; Zicaro JP performed the literature review and edited the manuscript; Yacuzzi C, Astoul J and Costa-Paz M edited the manuscript; Martinez E performed the cadaver dissection for the figures; all authors approved the final draft of the manuscript.

**Conflict-of-interest statement:** All the authors have no conflict-of-interest.

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**S-Editor:** Wang DM

**L-Editor:** A

**P-Editor:** Wang DM

**REFERENCES**


Taneja AK, Miranda FC, Braga CA, Gill CM, Hartmann LG, Santos DC, Rosenberg LA. MRI features of the anterolateral ligament of the knee. Skeletal Radiol 2015; 44: 403-410 [PMID: 25427785 DOI: 10.1007/s00256-014-2052-x]


Rasmussen MT, Nitri M, Williams BT, Moulton SG, Cruz RS, Doman GJ, Goldsmith MT, LaPrade RF. An In Vitro


Complication of lengthening and the role of post-operative care, physical and psychological rehabilitation among fibula hemimelia

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Specialty type: Orthopedics
Provenance and peer review: Invited article; Externally peer reviewed.
Peer-review model: Single blind
Peer-review report's scientific quality classification
  Grade A (Excellent): 0
  Grade B (Very good): B, B
  Grade C (Good): 0
  Grade D (Fair): 0
  Grade E (Poor): 0
P-Reviewer: Byeon H, South Korea; Velázquez-Saornil J, Spain
Received: March 23, 2022
Peer-review started: March 23, 2022
First decision: April 13, 2022
Revised: April 27, 2022
Accepted: July 25, 2022
Article in press: July 25, 2022
Published online: August 26, 2022

Abstract

There is a clear clinical need for efficient physiotherapy and rehabilitation programs during and after bone lengthening and reconstruction for gaining the optimal effect and also prevention or treatment of lengthening side effects. Pin tract infection is the most prevalent side effect during lengthening which could be prevented and treated initially via proper wound care. Muscle contractures are typically a consequence of the generated tension on the distracted muscle. It can be managed by physiotherapy initially and surgically in later severe stages. Furthermore, it is essential to avoid muscle contracture development, which is the demonstration of the imbalanced muscle appeals on the joint to inhibit the following subluxation. The knee is the furthermost affected joint by the aforementioned problem due to the inherent lack of ligamentous and bony stability. Joint stiffness is the other possible unfavorable effect of lengthening. It happens because of extensive muscle contractures or may possibly be attributed to rigidity of the joint following the amplified pressure on the joint surface during the process of lengthening. Physiotherapy and occupational therapy including endurance and strength exercise as well as stretching play an important role during the rehabilitation periods for the prevention and also the treatment of muscle contracture and the following deformity and also joint stiffness. Likewise,
the effect of mental and physical rehabilitation programs should not be overlooked.

**Key Words:** Fibular hemimelia; Rehabilitation; Reconstruction; Lengthening

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**Core Tip:** Difficulties that occur during limb lengthening are not avoidable. Pin tract infections are considered the most common adverse effect of lengthening which should be prevented through prophylaxis and treated as soon as possible when occurred. Muscle contractures are usually a result of the tension generated on the muscle due to distraction. It can be managed by physiotherapy initially and surgically in later severe stages. Subluxation or dislocation during lengthening may have been attributed to the preexisting joint instability or imbalanced muscle tension that developed during lengthening. It often happens in the knee joint posteriorly.

**INTRODUCTION**

Fibular hemimelia (FH) is considered the most common long bones deficiency and includes an extensive spectrum of anomalies, from a slight partial fibular shortening to a whole lack of fibula, and associated defects of the foot, and ankle, tibia, femur, and even hand abnormality[1].

With respect to the numerous deformities among fibular insufficiency as well as its relationship with postaxial hypoplasia, decision-making and strategies of treatment must be personalized[2]. Treatment choices consist of non-surgical management with shoe lift and orthotic devices; limb preservation, which includes limb elongation strategies; or amputation followed by lifetime prosthetic use. The aforementioned recommended managements are principally hooked on the harshness of the amount of limb length discrepancy, the foot deformity and deficiency, and the potential for achieving the functional and plantigrade foot[3]. The optimal treatment of FH has been controversial for a long time. Amputation along with prosthetic fitting has been recommended as an effective method in the management of FH in early studies and they also use to believe that patients may be more satisfied with amputation and prosthesis with no need for multiple surgeries to correct the deformities and then lengthen the usual major limb length discrepancies[4].

Unfavorable side effects have inundated limb-lengthening procedures since the first introduction for lengthening of the lower limb in 1905[5]. High obstacle rates, mostly bone-healing related, turn into the hallmark of the conservatively accepted aforementioned technique[6]. Along with the introduction of physiological-based approaches to elongation established by Ilizarov[7] in 1988 and according to the biology and physiology of soft tissue as well as bone regeneration under the tension and stretching condition, bone healing problems and complications have developed substantially less and the treatment goals are mostly achieved[8].

It did not take long before the great revolution of Ilizarov’s principles of external fixation, became the main pillar of reconstruction and lengthening. This improved the results of limb preservation and reconstruction presenting an attractive alternative to amputation[9]. Over time and as surgeons become more interested in limb preservation, lengthening, and reconstruction, several studies have been conducted on the effects of post-operative care and rehabilitation on the final outcome of reconstructive surgical approaches[10,11]. Since the Ilizarov technique is slow and gradual through daily physiologic changes in the soft tissues and bone, many potential difficulties develop during the distraction as well as fixation periods. Some of the aforementioned difficulties could be solved during the lengthening procedure[6]. In this perusal, we reviewed the literature to find the current post-operative care and rehabilitation programs during and after limb lengthening and reconstruction.

**PIN TRACT INFECTION**

Pin tract infections are considered the most common adverse effect of lengthening or even an almost inevitable obstacle in using external apparatus with various rates of 5% to 100% which is the result of
Muscle contracture is frequently a consequence of the over tension on the muscle following distraction[28]. They often have a tendency to happen in the over-powering muscle group. It goes back to the strength difference between extensors and flexors[29]. Knee flexion and ankle plantarflexion contracture during the lengthening of the tibia, the most common site of lengthening among fibula hemimelia, occurs because of the triceps surae muscle’s resistance to lengthening because of their large muscle mass and strength[30]. In some cases, who have a simultaneous proximal focal deficiency, which is accompanied by fibular hemimelia in 50% to 80%, the second stage of lengthening from femoral bone is desirable[31]. In these cases, the hamstrings are the bulkiest and largest muscle group. The hamstring contracture leads to the moving back of the leg (hip extension) and the knee to bend (knee flexion)[32].

The muscles that cross two joints are frequently involved in contractures because they contain fibers of numerous extents as opposed to muscles crossing a single joint and have fibers of the same extent[33]. They would cause tension deviations in similar muscles. Muscle tension is a mechanism of stimulating regeneration in muscle during the lengthening procedure. Muscles that pass through two joints may contain a variance proportion of histogenesis in comparison to muscles crossing a single joint[34]. Moreover, it may be attributed to the differences in the maximum histogenesis rate and potential between bone and muscle[35].

The other etiologic concern is the muscles or tendons’ transfixion by the pins of the apparatus[36]. It would be amplified via transfixed pins, the longitudinal clump of numerous pins in the single plane as well as the thick pins’ diameter. Transfixated fascia and tendons lead to joint motion restriction more than transfixated muscles[36].

Therefore, muscle contracture prevention is an inevitable portion of the elongation process. The initial preventive methods include fixation across joints, splinting, and physiotherapy[37]. Physiotherapy has been expected to motivate passive stretching movements for the most involved muscles. Moreover, it is not enough to stretch the muscle only at one end, due to the fact the aforementioned muscle typically crosses two joints. For instance, regarding the triceps surae, while the knee is flexed, the foot should be motivated to dorsiflex maximally. Afterward, the knee would be extended passively, as the ankle is dorsiflexed[38,39]. The patient must be instructed and motivated to repeat the aforementioned movements during the day[40]. Electrical stimulation, as well as active exercises, are approved to improve muscle regeneration[41]. There are several reports which have shown the positive role of continuous passive motions (CPM). Many studies have demonstrated the encouraging effect of passive motion in improving the knee flexion contracture[42,43]. CPM has also some proven hopeful effects in planter flexion contracture of the ankle which is frequently seen following tibia lengthening[44].

The principles of contracture prevention would work if they have been maintained for at least six hours each day. It is far from the mind that most cases would exercise their muscles that much[45,46].

Trigger point dry needling is suggestive management that would reduce the pain during the physiotherapy and stretching process. This hypothesis has been supported by several investigations demonstrating that muscle damage identified by magnetic resonance imaging after the application of dry needling over the spasmended muscle was associated with post-needling induced pain[42]. They have associated the presence of post-needling with the number of local twitch responses elicited during the needling therapy. Moreover, Gattie et al[47] conducted an interesting meta-analysis that displayed low to moderate evidence suggesting that dry needling, when applied by physical therapists, is superior to each treatment solely. This may reduce the pain and so fascinate the stretching progression.
SUBLUXATION/ DISLOCATION

Dislocation or subluxation of the adjacent joint frequently occurs during lengthening[48]. It may have been attributed to the preexisting joint instability. For example, the anterior cruciate ligament deficiency almost always occurs in the fibula hemimelia state due to femoral notch narrowing[49,50]. The imbalanced muscle pressure that developed during elongation might conduce subluxation, even in the lack of preoperative instability; this particularly happens in the knee[51,52]. Therefore, it is fundamental to avoid muscle contracture presentation.

The knee is the most frequently affected joint because of the inherent deficiency of bony and ligamentous stability[28]. It also should be mentioned that if there is a body segment with a hypomobility (deficit of movement), the nearest segment (joint) will assume that deficit creates hypermobility (increased movement, and therefore the possibility of subluxation) thus creating a compensatory mechanism automatically and involuntarily by the patient.

The subluxated joint may be improved using stretching physiotherapy of the distorting muscle force. It is worth mentioning that physiotherapy would help in the early stages and among milder cases. Traction is another way of management[53]. For the cases of complete dislocation as well as the more severe and persistent subluxation, the apparatus should be extended across the joint to distract and then relocate it gradually or immediately. Moreover, tendon or capsular releases or reapplication of the Ilizarov may be needed[54].

Figure 1 Pin tract infection. A: Healthy healing of pin tract site; B: Infection of pin tract site.

Figure 2 Lateral view of the tibia and associated muscles. A: Before lengthening. Gastrosoleus muscles and Achilles tendon; B: After lengthening of tibia. Ideally the muscle should lengthen to the same extent as the bone; C: Knee flexion contracture. This occurs when knee extension is not maintained throughout lengthening. A relative shortening of the muscle to the new bone length has been produced; D: Equinus contracture of ankle. This occurs when ankle dorsiflexion is not maintained during lengthening.
JOINT STIFFNESS

Joint rigidity is usually known as a late-onset complication\cite{55}. This happens because of long-term muscle contractures or can be attributed to rigidity of the joint following the amplified pressure on the joint surface during the elongation process\cite{56}. If a joint is being assumed at the risk of residual rigidity while the elongation device was still on, it should be extended across the joint, and the joint can be distracted afterward. Following that the device can be used to mobilize the joint prior to its removal \cite{57}. The severity of adverse effects can be different according to the created functional limitation. Apparently, 15° loss of ankle dorsiflexion or knee extension is much more significant in comparison to the same motion limitation in ankle plantar flexion and knee flexion\cite{58}.

PSYCHOLOGICAL AND MENTAL REHABILITATION

Many experienced pediatric orthopaedics have stated that quality of life will increase as the child grows up\cite{22,59}. The higher quality of life in adults may be attributed to psychological reasons and musculoskeletal development\cite{60}. To describe more precisely, children and their parents are generally under the impression that surgery will make their appearance, daily function, and other physical aspects normal and like healthy individuals\cite{61}. They sometimes confuse this defect with a simple bone fracture and expect it to be completely repaired with surgery. But as these patients age, they will become more realistic about their malformation and learn to adjust their lives to their disease\cite{22}. Therefore, more involved in routine daily activity and report a higher quality of life when being surveyed. Through much literature review, we have come to the conclusion that educating parents about the fact that FH has a range of problems and that the patients who choose any management method will never be as skeletal as their peers are ultimately effective in their satisfaction\cite{61}.

CONCLUSION

Limb salvage and lengthening is a speedily growing approach to orthopaedic surgery among bone deficient cases. There are some unavoidable adverse effects. Pin Tract Infection could be extensively prevented via post-operative wound care and cleaning. Muscle contracture could be prevented and managed by physiotherapy in the early stages and surgically in later severe stages. Subluxation/dislocation would be treated by stretching the deforming muscle force during the physiotherapy procedure. Moreover, if a joint is being assumed at the risk of residual rigidity while the elongation device was still on, it should be extended across the joint, and the joint can be distracted afterward. Following that the device can be used to mobilize the joint prior to its removal. Therefore, the aforementioned issues during or after lengthening could be prevented extensively through proper physiotherapy and occupational therapy including endurance and strength exercise as well as stretching programs. Psychological Rehabilitation would also improve the long-term quality of life and patients' satisfaction.

FOOTNOTES

Author contributions: Salimi M performed the majority of the writing; Mirghaderi SP prepared the figures; Salimi A performed data accusation and writing; Sarallah R and Khanzadeh S provided the input in writing the paper; Javanshir S designed the outline and coordinated the writing of the paper.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

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S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP
REFERENCES


21. Calder PR, Faithful M, Goodier WD. The role of external fixation in paediatric limb lengthening and deformity correction.
Salimi M et al. Complication of lengthening and physiotherapy


Clinical and Translational Research

Pyroptosis-related genes play a significant role in the prognosis of gastric cancer

Shi-Hao Guan, Xin-Yu Wang, Ping Shang, Qian-Cheng Du, Ming-Zhi Li, Xiao Xing, Bin Yan

**Abstract**

**BACKGROUND**
Pyroptosis is an inflammatory form of programmed cell death, which has been shown to be related to the prognosis of many tumors. However, its role in gastric cancer (GC) is not fully understood.

**AIM**
To evaluate the expression of pyroptosis-related genes in GC and its correlation with prognosis.

**METHODS**
We constructed prognostic multigene markers of differentially expressed genes associated with pyroptosis by least absolute contraction and selection operator Cox regression. The risk model was analyzed by Kaplan-Meier curve, two-sided log-rank test and functional enrichment analysis.

**RESULTS**
Sixty-three pyroptosis-related genes were differentially expressed in tumor tissues and adjacent nontumor tissues. Based on these differentially expressed genes, 5 gene signature were constructed and all GC patients were classified into two risk groups. Kaplan-Meier survival curve showed that the overall survival (OS) of patients in the high-risk group was significantly lower than that of the low-risk group. Multivariate Cox regression analyses showed that the risk score was an independent risk factor for OS. Receiver operating characteristic curve analysis confirmed the predictive ability of the model. External validation indicated...
increased OS in the low-risk group. The immune function and immune cell scores of the high-risk group were generally higher than those of the low-risk group.

CONCLUSION
Pyroptosis-related genes play a significant role in tumor immune microenvironment. This novel model, which contains 5 pyroptosis-related genes, is an independent predicting factor for OS in GC patients, and may help to evaluate the prognosis of GC.

Key Words: Gastric cancer; Pyroptosis; Gene signature; Overall survival

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Core Tip: This study aims to evaluate the expression of pyroptosis-related genes in gastric cancer (GC) and its correlation with prognosis. Based on 63 pyroptosis differentially expressed genes, 5 gene signature were constructed and all GC patients were classified into two risk groups. Kaplan-Meier survival curve showed that the overall survival (OS) of patients in the high-risk group was significantly lower than that of the low-risk group. Multivariate Cox regression analyses showed that the risk score was an independent risk factor for OS. The immune function and immune cell scores of the high-risk group were generally higher than those of the low-risk group. Similar results were obtained in external validation.

Citation: Guan SH, Wang XY, Shang P, Du QC, Li MZ, Xing X, Yan B. Pyroptosis-related genes play a significant role in the prognosis of gastric cancer. World J Clin Cases 2022; 10(24): 8490-8505
URL: https://www.wjgnet.com/2307-8960/full/v10/i24/8490.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i24.8490

INTRODUCTION
Gastric cancer (GC) is one of the most common malignant tumors of the digestive tract in the world. According to the data, there are approximately 1.03 million cases of GC, accounting for 5.6% of the total number of cancer cases. The incidence is approximately 11.1 per 100000, ranking fifth among all malignant tumors. There are approximately 782000 deaths from GC, accounting for 8.2% of all tumor-related deaths, with a mortality rate of approximately 8.2 per 100000; GC has the third highest death rate among cancers worldwide[1]. Almost two-thirds of GC cases occur in Asia (especially Japan, South Korea, and China). Compared with Japan and South Korea, China's early GC accounts for only 19.7%, and 40% of patients have no indications for radical surgery at the time of diagnosis[2,3]. There is significant heterogeneity in the response of GC patients to treatment. The treatment effect of advanced GC is limited, the median survival time is only about 1 year, and the prognosis has not been effectively improved[4]. Therefore, it is essential to find more targets, determine the treatment advantage population, and improve the efficiency of precise treatment of GC.

Pyroptosis is a kind of programmed cell death caused by inflammasomes, which is manifested by the continuous expansion of cells until the cell membrane ruptures, resulting in the release of cell contents and a strong inflammatory response[5]. The classic pathway of pyroptosis depends on the inflammatory caspase and gasdermines (GSDMs) protein family. The activated caspase cleaves the GSDMs protein and releases its N-terminal domain, which binds to membrane lipids and punches holes in the cell membrane. Perforating on the top causes the cell osmotic pressure to change and then swells until the cell membrane ruptures[6-8]. Pyroptosis is a crucial natural immune response of the body, which plays a vital role in fighting infection. In recent years, increasing studies have shown that it also plays a significant role in the development of tumors[9]. Rébé et al[10] found that Liver X receptor ligand-induced pyroptosis occurs in colon cancer cells. LncRNA GAS5 inhibits the glucocorticoid receptor complex and triggers the formation of inflammasomes, which in turn activates the inflammatory pathway and induces apoptosis in ovarian cancer cells[11]. Lipopolysaccharide (LPS) can induce pyroptosis and play an important role in the carcinogenesis of Barrett's esophagus. LPS activates and activates the NOD-like receptor protein 3 in Barrett cells to enhance the secretion of proinflammatory cytokines, including interleukin (IL)-1β and lactate dehydrogenase (indicators of pyroptosis)[12].

Therefore, we conducted a systematic study on pyroptosis genes. We constructed a prognostic polygene signature of differentially expressed genes (DEGs) related to pyroptosis based on the mRNA levels of pyroptosis-related genes, and externally verified. On this basis, we further carry out functional enrichment analysis to explore its potential immune mechanism. The purpose of this study is to classify GC with pyroptosis-related regulatory factors to construct a scoring model to predict the prognosis of GC and explore the prognostic value of these genes, to provide new ideas for the clinical treatment of
MATERIALS AND METHODS

Data collection
As of August 23, 2021 RNA sequencing (RNA-seq) data (n = 373) and clinical features data (n = 401) for GC information were downloaded from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/repository), and the RNA-seq data including 343 GC tissues and 30 adjacent nontumor tissues. A total of 432 GC patients information of the external validation cohort were downloaded from Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). Patients without survival information were excluded from further analysis. All above datasets are publicly available. Therefore, this study did not involve relevant ethics and strictly follows the relevant database access policies and guidelines.

Obtain differentially expressed genes related to pyroptosis
We searched for pyroptosis-related genes from AmiGO2 (http://amigo.geneontology.org/amigo/Landing), Gene-National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/gene/) and Gene Set Enrichment Analysis (http://www.gsea-msigdb.org/gsea/index.jsp), deleted duplicate entries, and finally identified 119 pyroptosis-related genes (the detailed data are available in Supplementary material). The data in TCGA database were normalized to fragment per kilobase million (FPKM) values before comparison. The “limma” package was used to identify DEGs with a P < 0.05. The DEGs were marked as follows: a P < 0.05, b P < 0.01, and c P < 0.001. The protein–protein interaction (PPI) network of DEGs was constructed with the Search Tool for the Retrieval of Interacting Genes (STRING) version 11.5 (https://string-db.org/), and the highest confidence interval was selected. The “reshape2”, “igraph” package was used to construct the co-expression network of pyroptosis-related genes.

Construction and validation of a prognostic pyroptosis-related gene signature
Univariate Cox regression analysis was performed to assess the association between genes and survival status in the TCGA cohort, selecting 0.005 as the cutoff P value. To minimize the risk of overfitting, using the least absolute shrinkage and selection operator (LASSO) Cox regression to narrow down the candidate genes and develop a prognostic signature. The ‘glmnet’ package in R software was used to select variables and shrink them by the LASSO algorithm, and the penalty parameter (λ) was decided by using the minimum criteria. The risk score was reckoned after centralization and standardization of the TCGA data. The risk score formula is as follows: Risk Score = Σ Xi × Yi (X: coefficients, Y: gene expression level). The TCGA cohort were divided into two subgroups pursuant to the median risk score. The overall survival (OS) time of the two subgroups was compared by Kaplan-Meier analysis. Principal component analysis (PCA) and t-distributed stochastic neighbor embedding (t-SNE) were performed using the “prcomp” function in the “stats” R package according to the gene expression in the gene profile. The “survival”, “survminer” and “time-receiver operating characteristic (ROC)” R packages were employed to perform a 5-year ROC curve analysis. We used the GEO cohort for validation. The expressions of pyroptosis-related gene were also normalized by the “scale” function, and the risk score was measured by the same formula as the TCGA cohort. By adopting the median risk score from the TCGA cohort, patients in the GEO cohort were also divided into low-risk and high-risk subgroups, and these subgroups were compared to validate the gene model.

Independent prognostic analysis of risk score
We figure out the clinical information of patients from the TCGA cohort and GEO cohort, including age, gender, tumor differentiation, depth of invasion, and lymph node metastasis. Prognostic analysis of these variables combined with risk scores. Univariate and multivariate Cox regression models were applied for analysis.

Functional enrichment analysis
The TCGA cohort were divided into two subgroups pursuant to the median risk score. We set $|\log_{2}\text{FC}| \geq 1$ and false discovery rate (FDR) < 0.05 as the criteria for screening DEGs between the low-risk group and the high-risk group. Founded on these DEGs, Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional analysis were performed by applying the “cluster Profiler” package. The “gsva” package was applied to perform single sample gene set enrichment analysis (ssGSEA) to calculate the infiltration scores of 16 kinds of immune cells and the activities of 13 immune-related pathways.

Statistical analysis
One-way analysis of variance was used to compare gene expression levels between adjacent nontumor
tissues and GC tissue, while categorical variables were analyzed using Pearson chi-square test. The Kaplan-Meier method and the two-sided log-rank test were used to compare the OS of patients between subgroups. Univariate and multivariate Cox regression analysis were performed to estimate the risk model’s independent prognostic value in both TCGA cohort and GEO cohort. The immune cell infiltration and immune pathway activation between the two groups were compared by Mann–Whitney test with corrected $P$ values. All statistical analysis was done using R software (version 4.1.0).

**RESULTS**

**Identification of DEGs between adjacent nontumor tissues and tumor tissues**

The overall flow chart is depicted in Figure 1. We compiled the genes of 30 adjacent nontumor tissues and 343 tumor tissues in the TCGA database and compared the expression levels of 118 genes related to pyroptosis. We identified 63 DEGs ($P < 0.05$). The RNA levels of these genes were presented in heatmap, among them, 8 genes (CHMP6, NR1H2, CASP9, TXNIP, ELANE, CRTAC1, TUBB6 and NFE2L2) were downregulated, while the other 55 genes were abundant in the tumor group (Figure 2A). To further explore the interaction of these DEGs, we conducted a PPI analysis. The minimum interaction score required for PPI analysis is set to 0.900 (the highest confidence level), the results show that TP53, PYCARD, CASP8, NFKB1, CHMP2A, CHMP6, TUBB6 and NFE2L2 were downregulated, while the other 55 genes were abundant in the tumor group (Figure 2A). We further compared the OS time between the two clusters and found that the survival rate of the C1 cluster was higher than that of the C2 cluster, and the difference was statistically significant ($P = 0.025$, Figure 3B). Gene expression profile and clinical features including tumor differentiation degree, gender (≤ 65 years or > 65 years), stage, depth of tumor invasion, lymph node metastasis, and distant metastasis were all shown in a heatmap. In the figure, the difference in the degree of tumor differentiation was diversely distributed between the two clusters (Figure 3C).
Construction of a prognostic model in the TCGA cohort

Univariate Cox regression analysis was used for preliminary screening of survival-related genes. Five genes that met the standard of P < 0.005 (ELANE, IL1A, CRTAC1, NFE2L2, TUBB6) were retained for further analysis (Figure 4A). By performing LASSO Cox regression analysis, 5 genes signature were constructed based on the optimal value of λ (Figure 4B and C). The risk score is calculated as follows: Risk score = (0.209 * ELANE exp.) + (0.255 * IL1A exp.) + (0.177 * CRTAC1 exp.) + (-0.326 * NFE2L2 exp.) + (0.123 * TUBB6 exp.). The GC patients were equally divided into low-risk and high-risk subgroups according to the median cutoff value (Figure 4D). PCA and t-SNE analysis showed the patients with different risk groups were well distributed into two clusters (Figure 4E and F). The patients with high risk had more deaths and shorter survival time than those with low risk (Figure 4G). Consistently, the Kaplan-Meier curve revealed that patients in the high-risk group had a significantly associated with poor OS (P = 0.003, Figure 4H). Employing time-dependent ROC curves to evaluate the sensitivity and specificity of the prognostic model, we found that the area under the curve (AUC) was 0.627 for 1 year, 0.655 for 3 years, and 0.669 for 5 years (Figure 4I).

Validation of the risk model in the GEO cohort

A total of 431 GC patients from the GEO cohort for external verification. According to the median risk score in the TCGA cohort, 247 patients in the GEO cohort were classified as high-risk group, while the other 184 patients were classified as low-risk group (Figure 5A). PCA and t-SNE analysis confirmed that patients in the two subgroups were distributed in discrete directions (Figure 5B and C). Similar to the results of the TCGA cohort, patients in the low-risk subgroup survived longer and lower mortality compared with those in the high-risk subgroup (Figure 5D). And the Kaplan-Meier analysis also showed that the survival time of the high-risk group was shorter (P = 0.008, Figure 5E). Besides, ROC curve analysis of the GEO cohort shows that the AUC was 0.561 for 1-year survival, 0.575 for 3-year survival, and 0.600 for 5-year survival (Figure 5F).

Independent prognostic value of the risk model

We used univariate and multivariate Cox regression analysis to assess whether the risk score was an independent prognostic predictor factor for OS. In univariate Cox regression analyses, the risk score was an independent factor predicting poor OS in both the TCGA and GEO cohorts (HR = 3.527, 95% CI: 2.103-5.914 and HR: 2.326, 95% CI: 1.544-3.505, Figure 6A and B). Multivariate analysis also suggested that after correction for other confounding factors, the risk score was a prognostic factor for the two groups of GC patients (TCGA cohort: HR = 3.445, 95% CI: 2.081-5.704, GEO cohort: HR: 2.117, 95% CI: 1.398-3.207, Figure 6C and D). Besides, we generated a heatmap of clinical characteristics for the TCGA cohort and found that the degree of tumor differentiation was differently distributed between the low-risk and high-risk subgroups (P < 0.05, Figure 6E).

Functional analyses in TCGA and GEO

To elucidate the molecular mechanism between subgroups classified by the risk model, the DEGs
Figure 3 Tumor classification based on the pyroptosis-related differentially expressed genes. A: Gastric cancer patients were classified into two clusters based on the consensus clustering matrix (k = 2); B: Kaplan-Meier overall survival curves for the two clusters; C: Heatmap and the clinical features of the two clusters classified by these differentially expressed genes (DEGs).

between the high-risk and low-risk groups were used to perform GO enrichment and KEGG pathway analyses. GO functional enrichment analysis showed that the DEGs from the TCGA cohort were significantly enriched in muscle system, extracellular matrix, and receptor ligand activity (P adjusted < 0.05, Figure 7A). KEGG pathway analyses also indicated that DEGs are rich in some classic pathways, including bone morphogenetic protein (BMP) and regulation of transmembrane receptor protein serine/threonine kinase signaling pathway and regulation of cell motility (P adjusted < 0.05, Figure 7B).

To further analyze the correlation between risk score and immune status, we used ssGSEA to compare the enrichment scores of 16 immune cells and the activities of 13 immune-related pathways in both cohorts. In the TCGA cohort, the high-risk subgroup usually has significant immune cell infiltration, especially dendritic cells (DCs), macrophages, mast cells, neutrophils, T helper 2 cells (Th2) and tumor infiltrating lymphocytes (TIL) (P adjusted < 0.05, Figure 8A). Six immune-related pathways were validated in the TCGA cohort, except for the APC co inhibition and major histocompatibility complex (MHC) class I pathway, the activities of the other four immune pathways in the high-risk group were higher than those in the low-risk group (P adjusted < 0.05, Figure 8B). When evaluating the immune status in the GEO cohort, a similar conclusion was reached (P adjusted < 0.05, Figure 8C and D).
Figure 4 Construction of risk signature in The Cancer Genome Atlas cohort. A: Univariate Cox regression analysis of overall survival (OS) for each pyroptosis-related gene, and 23 genes with $P < 0.001$; B and C: The results of the least absolute contraction and selection operator (LASSO) Cox regression.
indicated that there were 11 OS-related genes; D: Distribution of patients based on the median value of risk score; E and F: Principal component analysis (PCA) plot and t-distributed stochastic neighbor embedding (t-SNE) analysis founded on the risk score; G: The distributions of OS status, OS and risk score for each patient; H: Kaplan-Meier curves for the OS of patients in the high-risk and low-risk groups; I: Area under the curve (AUC) of time-dependent receiver operating characteristic (ROC) curves demonstrated the sensitivity and specificity of the risk score.

Figure 5 Validation of the risk model in the Gene Expression Omnibus cohort. A: Distribution of patients in the Gene Expression Omnibus (GEO) cohort based on the median risk score in The Cancer Genome Atlas (TCGA) cohort; B and C: Principal component analysis (PCA) plot and t-distributed stochastic neighbor embedding (t-SNE) analysis for gastric cancer (GC) patients in the GEO cohort; D: The distributions of overall survival (OS) status, OS and risk score for each patient in the GEO cohort; E: Kaplan-Meier curves for comparison of the OS between low-risk and high-risk groups in the GEO cohort; F: Time-dependent receiver operating characteristic (ROC) curves for GC in the GEO cohort.
DISCUSSION

In the present study, we studied the expression of 118 pyroptosis-related genes in GC tissues and their association with OS. First, GC patients were classified according to the pyroptosis-related DEGs. However, the two clusters did not show significant differences in clinical characteristics. To create a better clinical application, we constructed a new prognostic signature of 5 pyroptosis-related genes through Cox univariate analysis and LASSO Cox regression analysis, and verified it in an external cohort.

Pyroptosis is a form of programmed cell death. Recent studies have shown that pyroptosis has become a new hot spot in cancer research, because it is closely related to the occurrence and development of cancer and may affect various stages of cancer. It also plays different roles in many cancers[13]. Cell pyroptosis promotes the secretion of proinflammatory factors. On the one hand, chronic inflammation caused by pyroptosis can form a microenvironment suitable for tumor cell growth, thereby promoting tumor growth, including immunosuppression, proliferation, angiogenesis, and metastasis. On the other hand, it can maintain intestinal barrier integrity to suppress the occurrence of tumor development[14,15]. It has the effect of inhibiting tumor growth in ovarian cancer, colorectal cancer, and liver cancer[11,16,17], but has a bidirectional effect on breast cancer[18]. However, the effect of pyroptosis on the prognosis of GC is still unclear. Therefore, we explored as many genes as possible related to pyroptosis and found 5 pyroptosis-related genes (ELANE, IL1A, CRTAC1, NFE2L2, and TUBB6) with significantly differentially expression in GC and related to overall survival.

ELANE encodes neutrophil elastase, which is a protease packaged in the primary particles of neutrophil precursors[19]. Kambara et al[20] proved that the lysis and activation of gosdermin D(GSDMD) in neutrophils can be mediated by ELANE, and the efficiency of inducing cell pyroptosis is the same as that of gosdermin D N-terminal fragment (GSDMD-cNT). A recent study showed that ELANE proteolysis releases the CD95 death domain, which interacts with histone H1 to selectively kill cancer cells with the least toxicity to noncancer cells[21]. Pyroptosis depends on the activation of caspase-1 family members and leads to the release of interleukin-1 family cytokines. IL-1A, as an important member of the IL-1 family, is a proinflammatory cytokines, on the one hand, participates in the transformation, growth, invasion, and metastasis of malignant tumors, on the other hand, it can activate the body’s immune system to limit tumor growth[22]. In the terminal differentiation process of human keratinocytes in vitro, multiple steps are involved in pyroptosis, among which the expression levels of pro-inflammatory IL-1A and IL-1B and pyroptosis pore-forming GSDMD are downregulated[23]. Recent studies have shown that genetic variants of IL-1A single nucleotide polymorphisms affect the risk of ovarian cancer, and genetic variants in the IL-1A gene region lead to susceptibility to GC[24,25]. Cartilage acid protein 1 (CRTAC1) is a novel human marker that can be used to distinguish human chondrocytes from osteoblasts and mesenchymal stem cells. Sun et al[26] found that pyroptosis markers (NLRP3, active Caspase-1, pro-Caspase-1, and GSDMD) can be induced in human lens epithelial cells by ultraviolet B (UVB) irradiation, and the downregulation of CRTAC1 significantly reversed the UVB induced cell pyroptosis. At present, there are no studies on pyroptosis and CRTAC1 in GC, but these studies may provide new findings for prognostic markers of GC. NFE2L2 is involved in the coding of β-tubulin, which forms microtubules and participates in the cytoskeleton, and biological functions such as cell division, differentiation and migration, and intracellular transport[29]. The experiment of Salinas et al[27] showed that knocking down the expression of TUBB6 can increase cell pyroptosis without changing IL-1β secretion, indicating that TUBB6 only affects the cell death aspect of this pathway, and may act downstream of caspase-1 activation. TUBB6 was once considered a potential mutation hotspot gene in colorectal cancer[31]. A recent GC whole-genome and transcriptome sequencing experiment found that some nonsynonymous mutations can lead to increased gene activity and mRNA expression (including TUBB6) Up-regulation suggesting that it may contribute to the wide spread of GC cells in the abdominal cavity[32]. All in all, these five genes are involved in pyroptosis and affect the progression of cancer cells, but whether it plays a role in GC requires more exploration.

Although the underlying mechanism of tumor susceptibility to pyroptosis has been a hot research area for some time in the past, the potential adjustment between tumor immunity and pyroptosis has remained elusive. We performed functional enrichment in GO, KEGG, and ssGSEA based on DEGs between different risk groups. In GO and KEGG analysis, biological pathways such as “muscle system”, “extracellular matrix”, “actin”, “regulation of cell motility”, and “BMP signaling pathway” were significantly enriched, emphasizing the role of pyroptosis-related genes in GC. We then performed the immune function and immune cell analysis between the two groups. Antigen-presenting cells, including DCs and T helper cells, can help present pyroptosis cells to T cells and co-stimulate T cells and paracrine
Figure 6 Univariate and multivariate Cox regression analysis of risk signature. A: Univariate analysis for The Cancer Genome Atlas (TCGA) cohort; B: Univariate analysis for the Gene Expression Omnibus (GEO) cohort; C: Multivariate analysis for the TCGA cohort; D: Multivariate analysis for the GEO cohort; E: Heatmap for the connections between clinicopathologic features and the risk groups.

DOI: 10.12998/wjcc.v10.i24.8490  Copyright ©The Author(s) 2022.
Figure 7 Functional analysis based on the differentially expressed genes in The Cancer Genome Atlas cohort. A: The most significant Gene Ontology (GO) enrichment in The Cancer Genome Atlas (TCGA) cohort (q-value: the adjusted P value); B: The most significant Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways in the TCGA cohort (q-value: the adjusted P value).
Figure 8 Comparison of the single sample gene set enrichment analysis scores for immune cells and immune pathways. A and B: Comparison of the enrichment scores of 16 types of immune cells and 13 immune-related pathways between different risk groups in The Cancer Genome Atlas.

DOI: 10.12998/wjcc.v10.i24.8490  Copyright ©The Author(s) 2022.
(TCGA) cohort; C and D: Comparison of the immune infiltration between different risk groups in the Gene Expression Omnibus (GEO) cohort. *P values were showed as: *P < 0.05, **P < 0.01, and ***P < 0.001.

Interferon triggers a subsequent response. Interestingly, immune function and immune cell scores were generally higher in the high-risk group than in the low-risk group in this study. In view of the limited data from GC and the characteristics of tumor heterogeneity, our results on immune infiltration provide some insights for further research. In addition, how the immune system related to pyroptosis plays a role in GC requires more in vitro and in vivo exploration and verification.

Our research aims to identify DEGs and establish a prognostic model associating pyroptosis with the prognosis of GC patients. Although we have conducted multigene and multidatabase verification, there are still limitations in this study that need to be considered. First, our prognostic model is constructed and verified through retrospective data from public databases. Further validation by in vitro and in vivo experiments with larger sample sizes is needed to better assess the relationship between prognostic model and pyroptosis. In addition, the association between risk score and immune activity needs to be mined or established for more GC immunotherapy data. Some single-cell sequencing results can explain the specific changes in the tumor microenvironment, which is also an aspect of our future attention.

CONCLUSION

In conclusion, our study defines a new prognostic model of 5 pyroptosis-related genes. The model was found to independently correlate with OS, providing an in-depth understanding of GC prognosis prediction and providing an important basis for future studies on the association between pyroptosis-related genes and GC immunity. The underlying mechanism between pyroptosis-related genes in GC and tumor immunity is still poorly understood, and further research is needed. Such challenges motivate us to continue our efforts.

ARTICLE HIGHLIGHTS

Research background
The expression of pyroptosis genes in gastric cancer (GC) has not been well analyzed for its correlation with the prognosis of GC and the immune infiltration of tumors.

Research motivation
This study provides some insights for a deeper understanding of GC pathogenesis.

Research objectives
To explore the correlation between pyroptosis genes and prognosis of GC.

Research methods
The authors constructed prognostic multigene markers of differentially expressed genes associated with pyroptosis by least absolute contraction and selection operator Cox regression. The risk model was analyzed by Kaplan-Meier curve, two-sided log-rank test and functional enrichment analysis.

Research results
Based on 63 pyroptosis differentially expressed genes, 5 gene signature were constructed and all GC patients were classified into two risk groups. Multivariate Cox regression analyses showed that the risk score was an independent risk factor for overall survival (OS). The immune function and immune cell scores of the high-risk group were generally higher than those of the low-risk group. Similar results were obtained in external validation.

Research conclusions
This novel model, which contains 5 pyroptosis-related genes, is an independent predicting factor for OS in GC patients. Pyroptosis-related genes play a significant role in tumor immune microenvironment.

Research perspectives
The underlying mechanism between pyroptosis-related genes in GC and tumor immunity is still poorly understood, and further research is needed.
ACKNOWLEDGEMENTS

Thanks to all public databases for sharing and uploading their data.

FOOTNOTES

Author contributions: Guan SH is the author of the main idea, conceived and designed the study, collected and analyzed the data, and wrote and revised the manuscript; Yan B conceived and designed the study, collected and analyzed the data and wrote the manuscript; Shang P and Du QC participated in drafting and revising the manuscript, and collected the data; Li MZ and Xing X revised the manuscript, and participated in the acquisition, analysis and interpretation of data; Yan B and Wang XY revised the manuscript and coordinated the research team; and All authors approved the final version of the manuscript.

Institutional review board statement: The data in the manuscript are all from public databases and do not involve the ethics of human and animal specimens.

Informed consent statement: The data in the manuscript are all from public databases.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: The datasets used during the current study are available from the corresponding author on reasonable request.

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Li X

REFERENCES


11 Li J, Yang C, Li Y, Chen A, Li L, You Z. LncRNA GAS5 suppresses ovarian cancer by inducing inflammasome


14 Zhou CB, Fang JY. The role of pyroptosis in gastrointestinal cancer and immune responses to intestinal microbial infection. *Biochim Biophys Acta Rev Cancer* 2019; 1872: 1-10 [PMID: 31059737] DOI: 10.1016/j.bcr.2019.05.001


Effects of propofol combined with lidocaine on hemodynamics, serum adrenocorticotropic hormone, interleukin-6, and cortisol in children

Song Shi, Lu Gan, Chun-Nv Jin, Rong-Fang Liu

**Background**
Children are a unique patient population. Anesthesia for pediatric abdominal surgery has long been achieved mainly with intravenous amiodarone and propofol alone or combined with other anesthetics. The incidence of complications and postoperative adverse reactions is relatively high owing to the imperfect development of various protocols for children. Choosing the most appropriate anesthesia program is an important means of reducing adverse reactions.

**AIM**
To explore the clinical value of propofol combined with lidocaine-assisted anesthesia in pediatric surgery.

**Methods**
A total of 120 children who underwent abdominal surgery at our hospital from January 2016 to March 2018 were selected and divided into groups A and B using the random number table method, with 60 patients in each group. Group B received ketamine for anesthesia, while group A received ketamine, propofol, and lidocaine. The pre- and postoperative heart rate (HR); mean arterial pressure (MAP); arterial oxygen saturation (SpO2); serum adrenocorticotropic hormone (ACTH), interleukin-6 (IL-6), and cortisol (Cor) levels; restlessness score during the recovery period [Paediatric Anesthesia Emergence Delirium Scale (PAED)]; and adverse reactions were compared between the two groups.

**Results**

**Abstract**

**BACKGROUND**
Children are a unique patient population. Anesthesia for pediatric abdominal surgery has long been achieved mainly with intravenous amiodarone and propofol alone or combined with other anesthetics. The incidence of complications and postoperative adverse reactions is relatively high owing to the imperfect development of various protocols for children. Choosing the most appropriate anesthesia program is an important means of reducing adverse reactions.

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**RESULTS**
The HR, MAP, and SpO\textsubscript{2} Level at five minutes before initiating anesthesia were compared between groups A and B, and the difference was not statistically significant ($P > 0.05$). At 10 and 20 minutes after anesthesia initiation, the HR and MAP were lower in group A compared with group B ($P < 0.05$). The differences in preoperative serum ACTH, IL-6, and Cor levels between groups A and B were not statistically significant ($P > 0.05$); however, the postoperative serum ACTH, IL-6, and Cor levels in group A were lower compared with group B ($P < 0.05$). Furthermore, the visual analog scale scores of group A at 2 h and 8 h postoperative were lower than those in group B, and the differences were statistically significant ($P < 0.05$). The mean PAED score in group A was lower than that in group B ($P < 0.05$), and the incidence of restlessness in group A was 23.33\% lower than that in group B (36.67 \%) ($P < 0.05$). The incidence of adverse reactions was lower in group A than in group B (6.25\% vs 16.25\%).

**CONCLUSION**

The anesthetic effect of propofol combined with lidocaine and ketamine in pediatric surgery was better than that of ketamine alone, and had less influence on hemodynamics and pediatric stress response indices, lower incidence of restlessness in the recovery period, and lower incidence of adverse reactions.

**Key Words:** Ketamine; Propofol; Lidocaine; Anesthesia; Children

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**Core Tip:** Propofol is a general anesthesia drug with fast onset, short duration, and fast recovery, but it can cause obvious pain during injection. Injection pain can be reduced by lidocaine combined with propofol. This study was to observe the anesthetic effect of propofol combined with lidocaine in pediatric surgery, and to provide guidance and basis for clinical practice.

**Citation:** Shi S, Gan L, Jin CN, Liu RF. Effects of propofol combined with lidocaine on hemodynamics, serum adrenocorticotropic hormone, interleukin-6, and cortisol in children. *World J Clin Cases* 2022; 10(24): 8506-8513

**URL:** [https://www.wjgnet.com/2307-8960/full/v10/i24/8506.htm](https://www.wjgnet.com/2307-8960/full/v10/i24/8506.htm)

**DOI:** [https://dx.doi.org/10.12998/wjcc.v10.i24.8506](https://dx.doi.org/10.12998/wjcc.v10.i24.8506)

**INTRODUCTION**

Pediatric abdominal surgery is a common type of pediatric surgery. Due to the poor tolerance of children and their susceptibility to crying and other adverse emotions, general anesthesia is typically used in clinical operations. Therefore, the selection of the most appropriate anesthetic drugs is of great significance for improving pediatric surgery outcomes. The best choice for anesthesia should not only meet the surgical requirements, but also allow children to recover in the shortest amount of time\cite{1}. At present, the compound anesthesia method is commonly used for pediatric general anesthesia, as ketamine is a deep analgesic drug that has little effect on children's respiratory and circulatory systems, and is commonly used in clinical settings. However, when the dosage is too high or the operation time is prolonged, ketamine is associated with increased adverse reactions. In recent years, propofol has been found to be a fast and effective general anesthesia drug with the advantages of rapid onset, short duration, and rapid recovery. However, propofol injections cause obvious pain during the process; therefore, lidocaine is combined with propofol to reduce the injection pain\cite{2}. This study observed the anesthetic effect of propofol combined with lidocaine in pediatric surgery to provide guidance and a basis for clinical practice.

**MATERIALS AND METHODS**

**Clinical data**

A total of 120 children who underwent abdominal surgery at our hospital from January 2016 to March 2018 were selected and randomly divided into groups A and B, with 60 patients in each group.

Group A included 39 boys and 21 girls aged 1–12 years (mean 6.3 ± 2.6 years) with an average weight of 22.6 ± 4.5 kg and an average operation time of 48.2 ± 9.0 min. Group B included 42 boys and 18 girls aged 1–12 years (mean 6.1 ± 3.2 years) with a mean weight of 23.0 ± 4.9 kg and an average operation time of 50.0 ± 10.2 min. Age, sex, weight, and operation time were compared between the two groups.
and the differences were not statistically significant \( (P > 0.05) \).

The inclusion criteria were as follows: (1) Children who underwent elective surgery; (2) children 1-12 years old; (3) children who underwent surgeries performed by the same group of anesthesiologists and surgeons; and (4) provision of written informed consent from the parents or guardians.

The exclusion criteria were as follows: (1) History of liver and kidney function diseases; (2) history of congenital heart diseases; (3) history of immune function and blood system diseases; and (4) history of major diseases associated with other systems.

This study was approved by the Medical Ethics Committee, and informed consent was obtained from the parents.

**Methods of anesthesia**

Phenobarbital and atropine were intramuscularly injected preoperatively, and ketamine (5 mg/kg) was used for the induction of anesthesia.

Participants in group A were administered ketamine, propofol, and lidocaine (ketamine 100 mg, propofol 60 mg, and lidocaine 40 mg mixed with 10 mL liquid) at 0.2–0.4 mL/kg/h via a pump, according to the individual intraoperative requirements of each child, and was discontinued 5 min before the end of the operation.

Participants in group B were administered 1% ketamine intravenously for anesthesia.

**Observation indicators and detection methods**

Heart rate (HR), mean arterial pressure (MAP), and arterial oxygen saturation (SpO\(_2\)) at 5 min before anesthesia (T0), 10 min after anesthesia (T1), 20 min after anesthesia (T2), and at the end of surgery (T3) were monitored and compared between the two groups. Serum adrenocorticotropic hormone (ACTH), interleukin-6 (IL-6), cortisol (Cor), emergence agitation score [Paediatric Anesthesia Emergence Delirium Scale (PAED)], and adverse reactions were observed before and after the operation.

The agitation score, which included five indicators (eye contact, purposeful behavior, awareness of the surrounding environment, uneasiness, and consolability), was recorded upon awakening. The higher the score, the more serious the anesthesia emergence delirium, and a PAED score ≥ 10 indicated restlessness.

Fasting venous blood samples (5 mL) were obtained and centrifuged at 2500 rpm, and the serum was extracted for testing. ACTH, IL-6, and Cor levels were measured using the electrochemiluminescence method. The concentration of IL-6 was measured using an enzyme-linked immunosorbent assay. All reagents were obtained from Nanjing Jiancheng Biological Products Co., Ltd., and strictly used in accordance with the manufacturer’s instructions.

The degree of postoperative pain was evaluated using the visual analog scale (10 points indicating the highest level of pain and 0 points indicating the lowest). According to the subjective pain scores of the children, the higher the score, the more serious the pain.

**Statistical analysis**

The measurement data were expressed as means ± SD, and the comparisons between groups were performed using two independent sample \( t \)-tests. The \( \chi^2 \) test was used for comparison of enumeration data between groups. A \( P < 0.05 \) indicated a statistically significant difference. All statistical analyses were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

**Comparison of hemodynamic indexes of two groups of children**

At T0, the HR, MAP and SpO\(_2\) Levels were compared between group A and group B, and the difference was not statistically significant \( (P > 0.05) \). At T1 and T2, HR and MAP in group A were lower than those in group B \( (P < 0.05) \) (Table 1).

**Comparison of serum ACTH, IL-6 and Cor levels in the two groups of children**

Preoperative serum ACTH, IL-6 and Cor levels in group A and group B were compared, and the difference is not statistically significant \( (P > 0.05) \). The levels of serum ACTH, IL-6 and Cor in group A were lower than those in group B after operation \( (P < 0.05) \) (Table 2).

**Comparison of the occurrence of restlessness during the wake of the two groups of children**

The score of PAED in group A was lower than that in group B \( (P < 0.05) \). The incidence of dysphoria in group A (23.33%) was lower than that in group B (36.67%) \( (P < 0.05) \) (Table 3).
Table 1 Comparison of hemodynamic indexes of two groups of children (mean ± SD)

<table>
<thead>
<tr>
<th>Groups</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (times/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A group</td>
<td>113.6 ± 8.2</td>
<td>120.5 ± 8.0</td>
<td>118.9 ± 7.5</td>
<td>115.5 ± 8.4</td>
</tr>
<tr>
<td>B group</td>
<td>115.0 ± 9.0</td>
<td>126.1 ± 7.4</td>
<td>125.0 ± 8.3</td>
<td>116.8 ± 8.0</td>
</tr>
<tr>
<td>F value</td>
<td>F1 = 13.025, F2 = 15.776, F3 = 8.169</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>P1 = 0.000, P2 = 0.000, P3 = 0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A group</td>
<td>85.2 ± 6.9</td>
<td>92.7 ± 5.5</td>
<td>92.0 ± 5.9</td>
<td>87.0 ± 5.3</td>
</tr>
<tr>
<td>B group</td>
<td>84.8 ± 6.5</td>
<td>96.0 ± 6.2</td>
<td>95.1 ± 6.8</td>
<td>89.1 ± 6.5</td>
</tr>
<tr>
<td>F value</td>
<td>F1 = 9.881, F2 = 13.764, F3 = 6.990</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>P1 = 0.000, P2 = 0.000, P3 = 0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>98.2 ± 0.6</td>
<td>97.7 ± 0.7</td>
<td>97.8 ± 0.6</td>
<td>98.0 ± 0.5</td>
</tr>
<tr>
<td>F value</td>
<td>F1 = 2.514, F2 = 6.395, F3 = 1.552</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>P1 = 0.168, P2 = 0.000, P3 = 0.351</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F1 and P1 are between groups, F2 and P2 are time effect, F3 and P3 are interaction. HR: Heart rate; MAP: mean arterial pressure; SpO₂: Arterial oxygen saturation.

Table 2 Comparison of serum adrenocorticotropic hormone, interleukin-6, and cortisol levels in two groups of children (mean ± SD)

<table>
<thead>
<tr>
<th>Groups</th>
<th>ACTH (ng/L)</th>
<th>IL-6 (ng/L)</th>
<th>Cor (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>12 h after operation</td>
<td>Preoperative</td>
<td>12 h after operation</td>
</tr>
<tr>
<td>A group (n = 60)</td>
<td>116.3 ± 15.7</td>
<td>130.2 ± 18.2</td>
<td>5.77 ± 2.01</td>
</tr>
<tr>
<td>B group (n = 60)</td>
<td>114.7 ± 13.5</td>
<td>145.0 ± 22.1</td>
<td>6.03 ± 2.28</td>
</tr>
<tr>
<td>t value</td>
<td>0.599</td>
<td>-4.004</td>
<td>-0.663</td>
</tr>
<tr>
<td>P value</td>
<td>0.551</td>
<td>0.000</td>
<td>0.509</td>
</tr>
</tbody>
</table>

ACTH: Adrenocorticotropic hormone; IL-6: Interleukin-6; Cor: Cortisol.

Table 3 Comparison of the occurrence of restlessness in the two groups of children during the waking period

<table>
<thead>
<tr>
<th>Groups</th>
<th>PAED score (points)</th>
<th>Incidence of restlessness, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A group (n = 60)</td>
<td>6.2 ± 2.5</td>
<td>14 (23.33)</td>
</tr>
<tr>
<td>B group (n = 60)</td>
<td>8.1 ± 2.9</td>
<td>22 (36.67)</td>
</tr>
<tr>
<td>t/χ² value</td>
<td>-3.844</td>
<td>4.104</td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>0.043</td>
</tr>
</tbody>
</table>

PAED: Paediatric Anesthesia Emergence Delirium Scale.

**Comparison of extubation time, awake time, and out-of-room time between the two groups of children**

The extubation time, awake time and leaving room time were compared between group A and group B, and the difference was not statistically significant (P > 0.05) (Table 4).
Shi S et al. Propofol combined with lidocaine anesthesia for children

**Table 4 Comparison of extubation time, awake time, and out-of-room time between the two groups (mean ± SD)**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pull-out time (min)</th>
<th>Wake time (min)</th>
<th>Off room time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A group (n = 60)</td>
<td>7.66 ± 1.84</td>
<td>10.59 ± 2.30</td>
<td>22.63 ± 3.81</td>
</tr>
<tr>
<td>B group (n = 60)</td>
<td>8.01 ± 1.92</td>
<td>11.36 ± 2.45</td>
<td>23.70 ± 3.54</td>
</tr>
<tr>
<td>t value</td>
<td>-1.019</td>
<td>-1.775</td>
<td>-1.594</td>
</tr>
<tr>
<td>P value</td>
<td>0.310</td>
<td>0.078</td>
<td>0.114</td>
</tr>
</tbody>
</table>

**Comparison of postoperative visual analog scale scores between the two groups of children**

The visual analog scale scores of group A at 2 h and 8 h after operation were lower than those of group B, and the differences were statistically significant (P < 0.05) (Table 5).

**Comparison of the incidence of adverse reactions in children between the two groups**

The incidence of adverse reactions in group A (6.25%) was lower than that in group B (16.25%) (P < 0.05) (Table 6).

**DISCUSSION**

Abdominal surgery is a common surgical procedure in pediatric patients. Due to their unique anatomical and physiological characteristics and relatively narrow airways, they have an increased risk of airway resistance during surgery. Therefore, pediatric patients consume more oxygen during surgery as they are prone to hypoxia. Moreover, children lack type I muscle fibers in the diaphragm and intercostal muscles; therefore, respiratory muscle fatigue can easily occur during breathing. Therefore, abdominal surgery is often performed with controlled mechanical breathing[3]. Due to the incomplete development of various physiological functions, imperfect development of the myocardial structure, poor myocardial systolic function, poor ventricular compliance, and thin abdominal walls in children, a series of complications can occur during the operation. Therefore, selecting the most appropriate anesthesia program is extremely important[4,5]. Historically, general anesthesia has been mainly used in pediatric abdominal surgery. General anesthesia can meet the needs of analgesia and sedation in children, and anesthetic equipment facilitates unobstructed breathing, effectively reducing the risk of reflex aspiration during the operation and ensuring the safety of the operation. However, in the process of general anesthesia, children’s bodies show obvious stress responses, and hemodynamic fluctuations usually occur. In order to reduce these adverse reactions, anesthesia is deepened by increasing the anesthetic and analgesic drug doses; however, this can lead to liver and kidney dysfunction. Therefore, adverse reactions such as delayed recovery, recovery, and postoperative respiratory depression are prone to occur[6,7]. In addition, it was also reported that general anesthesia could inhibit the cerebral cortex of children and was unable to block the conduction process of surgical nociceptive stimulation towards the sympathetic nerve, evidenced by an increase in the excitability of the sympathetic and adrenal medulla systems and hemodynamic fluctuation. Therefore, effective regulation of stress responses during anesthesia and achievement of good muscle relaxation and analgesia has been an important research topic in anesthesia for pediatric abdominal surgery[8,9].

In this study, propofol combined with lidocaine was used to assist general anesthesia in pediatric abdominal surgery. The role of propofol is to lower the level of consciousness and reduce body movements, as well as other general anesthetic actions in which the release and transmission of neurotransmitters play an important role. Among them, ligand-gated ion channels play an important role in general anesthesia, including γ-aminobutyric acid receptors, an important central nervous system inhibitory neurotransmitter which has a significant regulatory effect on the release of other neurotransmitters in the body. Propofol can inhibit the influx of ions in the body and inhibit the increased glutamate release caused by presynaptic membrane depolarization, which enhances the postsynaptic effect of γ-aminobutyric acid. Its role in respiratory smooth muscle function and the cardiovascular system is mediated by calcium channels. The decreased sodium-potassium-ATPase activity in the central nervous systems of children results in decreased electrochemical gradients caused by sodium ions and increased calcium ion concentration, which leads to increased acetylcholine content in the body, resulting in general anesthesia[10,11]. However, the required dose of propofol alone is high, and the analgesic effect is only observed in some children. Adverse reactions, including myocardial inhibition and blood pressure reduction can also occur[12].

Lidocaine, an amide-type local anesthetic, can be dispersed outside the blood vessels after entering human blood. The drug can react with hepatic microsomal mixed functional oxidase, an amide enzyme, and can be metabolized in multiple organs. The study also found that lidocaine used in anesthesia can inhibit human hippocampal neuronal sodium channels, thereby inhibiting central nervous system action potential, blocking nerve conduction, and causing a central inhibitory and anesthetic effect[13].
The combined use of these two anesthetics has an important synergistic effect because propofol acts directly on the blood vessel walls to release pain mediators. Meanwhile, lidocaine acts as a kinin inhibitor and stabilizer by blocking and thereby reducing the release of pain mediators [14]. The combined application of lidocaine and ketamine can enhance the sedative and hypnotic effect of propofol. Lidocaine inhibits propofol from binding to protein, which increases the amount of free propofol in the body and enhances the anesthetic effect of propofol. In addition, lidocaine can promote the recovery of sodium-potassium-ATPase activity in the sarcoplasmic reticulum, inhibit the overload of calcium ions, and reduce myocardial ischemia-reperfusion injury in children. When used together, the advantages of these two drugs complement each other, making it ideal for the application of surgical anesthesia [15].

Studies have shown that the levels of adrenocorticotropic hormone and cortisol in the body increase after the activation of the hypothalamic-pituitary-adrenal cortex axis in the perioperative period, which plays a role in promoting gluconeogenesis, proteolysis, and inhibiting inflammatory responses in the body. Cytokines are biologically active peptide compounds released by human immune effector cells, among which IL-6 is an important inflammatory response factor in the human body and has a regulatory effect on systemic inflammatory and immune responses. Cytokines increase significantly and then gradually decrease with decreased stress responses. The incidence of adverse reactions in group A was 6.25% lower than that in group B (16.25%), indicating that the application of propofol combined with lidocaine-assisted ketamine in pediatric abdominal surgery anesthesia can reduce the occurrence of adverse reactions to anesthesia. The advantage of this study is that our findings confirm the anesthesia effect and safety of propofol combined with lidocaine-assisted ketamine in pediatric abdominal surgery anesthesia, and provide a basis for identifying the optimal anesthesia plan for clinical pediatric abdominal surgery. Due to the limited number of children, prospective studies have not been carried out, and the follow-up time was short; therefore, multi-center studies with large sample sizes and randomized controlled trials are needed to validate our results.

CONCLUSION

In summary, the anesthetic effect of propofol combined with lidocaine-assisted ketamine for pediatric anesthesia was better than that of ketamine alone, with less influence on hemodynamics and pediatric stress response indices, lower incidence of restlessness during the recovery period, and lower incidence of adverse reactions.

ARTICLE HIGHLIGHTS

Research background

Pediatric abdominal surgery is a common type of pediatric surgery. Due to the poor tolerance of children and prone to crying and bad emotions such as crying, general anesthesia is mostly selected in the clinical operation. Therefore, reasonable choice of anesthetic drugs is of great significance to ensure
the effect of surgery in children.

**Research motivation**
In this study, the effect of propofol compound lidocaine-assisted anesthesia in pediatric surgery was observed.

**Research objectives**
This study aimed to explore the clinical value of propofol combined with lidocaine-assisted anesthesia in pediatric surgery.

**Research methods**
A total of 120 children who underwent abdominal surgery selected and divided into groups A and B using the random number table method, with 60 patients in each group. Group B received ketamine for anesthesia, while group A received ketamine, propofol, and lidocaine. The pre- and postoperative heart rate; mean arterial pressure; arterial oxygen saturation; serum adrenocorticotropic hormone, interleukin-6, and cortisol levels were compared between the two groups.

**Research results**
The anesthetic effect of propofol combined with lidocaine and ketamine in pediatric surgery is better than that of ketamine alone, and had less influence on hemodynamics and stress response indices, lower incidence of restlessness in the recovery period, and lower incidence of adverse reactions.

**Research conclusions**
The anesthetic effect of propofol combined with lidocaine and ketamine in pediatric surgery was better than that of ketamine alone.

**Research perspectives**
This study explored the clinical value of propofol combined with lidocaine-assisted anesthesia in pediatric surgery.

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**FOOTNOTES**

**Author contributions:** Shi S, Lu G and Liu RF designed this retrospective study and wrote the paper; Shi S and Liu RF contributed equally to this study, and considered as so-first authors; Shi S, Lu G, Liu RF and Jin CN were responsible for sorting the data.

**Institutional review board statement:** This study was reviewed and approved by the Affiliated Hospital of Hebei University.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors declare no conflict of interest.

**Data sharing statement:** No additional data are available.

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**S-Editor:** Wang JL

**L-Editor:** A

**P-Editor:** Wang JL
REFERENCES


13. Carroll NC. Clubfoot in the twentieth century: where we were and where we may be going in the twenty-first century. *J Pediatr Orthop B* 2012; 21: 1-6 [PMID: 21946867 DOI: 10.1097/BPB.0b013e32834a992]


Retrospective Study

Correlation analysis of national elite Chinese male table tennis players’ shoulder proprioception and muscle strength

Xue-Dong Shang, En-Ming Zhang, Zhen-Lei Chen, Lei Zhang, Jing-Hua Qian

Abstract

BACKGROUND
Shoulder is the most injured part in table tennis players, and it takes multiple roles in transmitting power and striking the center of the ball during the stroke. Proprioception is strongly correlated with high level of athletic performance. It is customary to assume that there is a correlation between proprioception and muscle strength and therefore proprioceptive assessment and rehabilitation is often neglected.

AIM
To investigate the correlation between isokinetic muscle strength and proprioception in the internal and external rotation muscle groups of elite Chinese male table tennis players, to provide reference for physical training and rehabilitation of elite table tennis players.

METHODS
A total of 19 national elite table tennis players from the Chinese National Table Tennis Team were recruited in this research. All of them had more than 10 years training experience and had participated major competitions such as the National Games and World Youth Championships. IsoMed 2000 was used to test the peak torque of internal and external rotation isokinetic concentric contraction of the athletes’ bilateral shoulder joints at low speed (60°/s) and high speed (180°/s)
respectively; IsoMed 2000 was used to conduct the Joint Position Reproduction test to evaluate the athletes’ proprioceptive ability capacity at low speed (60°/s) and high speed (180°/s) respectively. If the data satisfied the normal distribution, the correlation between the differences in peak torque and angles in different directions was analyzed using a Pearson simple linear model; otherwise, Spearman correlation analysis was used. The comparison of proprioceptive ability between the table tennis racket-holding hand and non-racket-holding hands was performed using independent samples t-test if the data satisfied a normal distribution; otherwise, the Mann-Whitney U test was used.

RESULTS
There was no direct linear correlation between the strength and proprioceptive correlation analysis at slow speed (60°/s) and fast speed (180°/s) in the racket-holding hand; At the slow speed (60°/s) and fast speed (180°/s), there was no correlation between muscle strength and proprioception in the non-racket-holding hand except for the internal rotation variable error (VE) and external rotation relative peak torque, which showed a moderate positive correlation ($r = 0.477, P < 0.05$), ($r = 0.554, P < 0.05$). The internal rotation’s constant error (CE) and VE were $1.06 \pm 3.99$ and $2.94 \pm 2.16$, respectively, for the racket-holding hand, and $-3.36 \pm 2.39$ and $1.22 \pm 0.93$, respectively, for the non-racket-holding hand; the internal rotation’s CE, VE of the racket-holding hand was lower than that of the non-racket-holding hand, and there was a highly significant difference ($P < 0.01$).

CONCLUSION
There was no correlation between muscle strength and proprioceptive function in the internal and external rotation of the racket-holding hand’s shoulder in elite Chinese male table tennis players. These results may be useful for interventions for shoulder injuries and for the inclusion of proprioceptive training in rehabilitation programs.

Key Words: Elite table tennis player; Shoulder; Proprioception; Muscle strength; Correlation analysis

INTRODUCTION
Table tennis players need to swing and hit the table tennis readily during training and competition. The shoulder joint takes multiple roles in transmitting power and striking the center of the ball during the stroke[1,2]. Studies have shown that the most injured part of table tennis players is the shoulder[3,4]. Therefore, investigating the correlation between shoulder joint’s strength and proprioception will not only help table tennis players improve technical movements and performance, but also will be beneficial for developing scientific and effective training and rehabilitation programs.

The term "Table Tennis Sense" was often mentioned in table tennis. In fact, the term "Table Tennis Sense" is synonymous with proprioception and coordination. Studies have shown that there is strong correlation between coordination and movement agility in ball sports, which means an athlete's ability to perform movements efficiently and quickly depends on the activation of the stabilizing muscles[5]. Meanwhile, there is a correlation between proprioception and high level of athletic performance[6]. With the elevation of shoulder and the increases of soft tissue tension, the proprioception of athlete will also change[7,8], which can affect the control of joint power output in end of range of motion, making shoulder proprioception particularly important. Proprioceptive tests are mainly based on kinesthetic and positional perception[9-11]. There are now many studies on proprioception of the ankle joint, but their methodological choices are flawed, such as not shielding visual interference[12]. Some studies have noted the problem and measured wrist sensory thresholds after excluding auditory and visual distractions[13], but exploration of kinesthetic and positional perception is still lacking in proprio-
In this study, the Joint Position Reproduction test (JPR)\cite{14-16} was selected to perform active JPR for internal and external rotation movements of the shoulder joint. Not only did it exclude other visual-auditory interference factors, but also meet the sport-specific requirements of table tennis. The aim of this study was to investigate the relationship between isokinetic muscle strength characteristics and proprioception in the internal and external rotation muscle groups of elite Chinese male table tennis players, and to provide a reference for physical training and rehabilitation of elite table tennis players.

**MATERIALS AND METHODS**

**Study design**
In this study, a cross-sectional survey in a descriptive study was used: IsoMed 2000 was used to test the peak torque of internal and external rotation concentric contraction of the athletes’ bilateral shoulder joints at low speed (60°/s) respectively; the JPR test was used to evaluate the athletes’ proprioceptive ability capacity. Since the proprioceptive ability is easily disturbed by many factors, the proprioceptive test was performed firstly, and then the isokinetic strength test was performed after 5 min rest.

**Study subjects**
Total 19 national elite athlete level table tennis players from the Chinese National Table Tennis Team were recruited into this research. All of them had more than 10 years training experience and had participated major competitions such as National Games of the People’s Republic of China and World Youth Championships. The basic information of the athletes is shown in Table 1.

**Proprioceptive test of shoulder joint**
The IsoMed 2000 (D. & R. Ferstl GmbH, Germany) was used to perform proprioceptive tests and isokinetic muscle strength on the athletes, and it has high reliability and validity according to numerous studies\cite{15,17}. As an important tool for studying the physiological basis of athletic ability and technical movement level, it can provide practical help in improving the technical movement of athletes and improving the scientific level of training. Along with the measurement of isokinetic muscle strength, many researchers have also used IsoMed 2000 to measure proprioception\cite{18,19} to assess an individual’s ability to actively repeat a reference position.

The starting position for internal and external shoulder rotation was 90 degrees of abduction, 90 degrees of elbow flexion and 30 degrees of humeral external rotation. The preset values were 40 degrees of external rotation and 20 degrees of external rotation (i.e., 10 degrees each of internal and external rotation under the starting position). The JPR for rotation was then performed sequentially, with a total of seven measurements (the first three for movement learning and the last four for the formal test). The subject actively moved the arm (shoulder joint) from the initial position to a predetermined target angle for 3 s, reminded the subject of this predetermined target position, and then returned to the neutral position. The subject then moved actively and pressed the pause button when the target angle was felt and the actual angle at this point was recorded. The shoulder proprioceptive ability was evaluated by comparing the difference between the actual position and the target position, and the evaluation indexes included constant error (CE), variable error (VE), and absolute error (AE). These indicators not only compare the magnitude and direction of error, but also evaluate the stability of error\cite{20,21} (Table 2).

**Isokinetic muscle strength testing of shoulder joints**
The IsoMed 2000 (D. & R. Ferstl GmbH, Germany) was used to perform isokinetic muscle strength test. To meet the sport-specific needs of table tennis players and to reflect the characteristics of the upper limb muscle strength at different speeds and to consider safety issues, the protocol was set to bilateral shoulders and slow speed was utilized firstly and then fast speed. The isokinetic muscle strength testing system was selected to quantify the strength of the internal and external shoulder rotation muscles for 5 repetitions at slow speed (60°/s) and 25 repetition at fast speed (180°/s), testing the dominant side and then testing the non-dominant side in the same way. The peak torque for external and internal rotation of the shoulder joint were selected bilaterally, resulting in a low velocity external rotation peak torque, a low velocity internal rotation peak torque, a high velocity external rotation peak torque and a high velocity internal rotation peak torque (Figure 1).

**Statistical analysis**
SPSS 20.0 (Statistical Package for Social Science, Chicago, IL, USA) software was used for statistical analysis and calculations. The Kolmogorov-Smirnov test was used to test the normality of the data. If the data satisfied the normal distribution, the correlation between the differences in peak torque and joint position at different directions was analyzed using a Pearson simple linear model. Otherwise, Spearman correlation analysis was used. The comparison of proprioception between the table tennis racket-holding hand and non-racket-holding hands was performed using independent samples t-test if
Table 1 Basic Information of the table tennis players (mean ± SD)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Body weight (kg)</th>
<th>Training experience (yr)</th>
<th>Level of athlete</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 19</td>
<td>17.87 ± 1.49</td>
<td>176.31 ± 4.19</td>
<td>66.67 ± 3.92</td>
<td>&gt; 10</td>
<td>National Elite athlete</td>
</tr>
</tbody>
</table>

Table 2 Calculation and significance of proprioceptive evaluation indicators of the shoulder joint

<table>
<thead>
<tr>
<th>Test</th>
<th>Evaluation index and its calculation methods</th>
<th>Meaning of the indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint position reproduction test of the shoulder joint</td>
<td>AE = (</td>
<td>Original error 1</td>
</tr>
<tr>
<td></td>
<td>CE = [(Original error 1) + (Original error 2) + ... + (Original error n)]/n</td>
<td>Taking the positives and negatives in direction into account to evaluate overall the error in the given direction of movement, reflecting whether the movement pattern overall exceeds or fails to reach the target.</td>
</tr>
<tr>
<td></td>
<td>VE = [(Original error 1-CE)^2 + (Original error 2-CE)^2 + ... + (Original error n-CE)^2]/n</td>
<td>Reflects the variability and consistency between the results of several position reproduction, regardless of the accuracy of the JPR.</td>
</tr>
</tbody>
</table>

AE: Absolute error; CE: Constant error; VE: Variable error; JPR: Joint Position Reproduction test.

Figure 1 Isokinetic muscle strength testing of shoulder joints with IsoMed 200.

The data satisfied a normal distribution. Otherwise, the Mann-Whitney U test was used. Significant differences were considered at $P < 0.05$ and highly significant difference were considered at $P < 0.01$. All indicators are expressed in mean ± SD. In this study, Cohen's $d$ was used to evaluate the effect size. The specific evaluation standard was: 0.1 represent a small effect size; 0.3 represent a medium effect size; and 0.5 represent a large effect size.
RESULTS

**Correlation analysis of the data from the proprioceptive test and isokinetic muscle strength test of the racket-holding hand**

**Slow speed:** The strength and proprioceptive correlation analysis at slow speed (60°/s) is shown in Table 3. The results indicate that there is no direct linear correlation between the two data groups.

**Fast speed:** The strength and proprioceptive correlation analysis at fast speed (180°/s) is shown in Table 4. The results of the study indicate that there is no direct linear correlation between the two data groups.

**Correlation analysis of the data from the proprioceptive test and isokinetic muscle strength test of the non-racket-holding hand**

**Slow speed:** At the slow speed (60°/s), there was no correlation between muscle strength and proprioception, etc., except for the internal rotation VE and external rotation relative peak torque, which showed a moderate positive correlation ($r = 0.477, P < 0.05$), as shown in Table 5.

**Fast speed:** At fast speed (180°/s), there was no correlation between forces and proprioception, etc., except for the internal rotation VE and the external rotation relative peak torque, which showed a moderate positive correlation ($r = 0.554, P < 0.05$), as shown in Table 6.

**Comparison of proprioceptive ability between the racket-holding hand and the non-racket-holding hand**

From the data exploration, the internal rotation’s CE and VE were 1.06 ± 3.99 and 2.94 ± 2.16, respectively, for the racket-holding hand, and -3.36 ± 2.39 and 1.22 ± 0.93, respectively, for the non-racket-holding hand. As seen in Table 7, the internal rotation CE, VE of the racket-holding hand was lower than that of the non-racket-holding hand, and there was a highly significant difference ($P < 0.01$).

DISCUSSION

In the present study, the index chosen for muscle strength is the peak torque, which represents the maximum torque of a muscle in the given direction of movement and has a high reliability. It is widely used in isokinetic muscle strength testing[22]. The observed metric for proprioception is the magnitude of the absolute error angle value, which quantifies abstract proprioception into data and also adequately represents the ability of position and kinesthetic perception, which is also considered as the gold standard in previous studies in the field of proprioception[14].

**The relationship between proprioception and muscle strength in the racket-holding hand**

From the study, no correlation was found between proprioception and muscle strength in the internal and external rotation of the shoulder joint of the racket-holding hand. However, because many of the receptors of proprioception, such as the muscle spindle and tendon organ, are in muscle tissue, it is customary to assume that there is a correlation between proprioception and muscle strength, especially after the onset of injury, when both muscle strength and proprioception are reduced[23,24]. However, in the present study, there was no significant difference ($P > 0.05$) between isokinetic muscle strength and proprioception in the shoulder joint of the racket-holding hand after the correlation coefficient was used to evaluate both in the fast and slow speed conditions, which is consistent with the findings of Wang[25-27].

The present study concluded that in shoulder motion, the muscle spindle is one of the main providers of joint position sensation in the middle range of joint motion, while the receptors located above the ligaments and joint capsule are not fully activated. They can only generate tension after being subjected to deformation to receive stimuli[23]. At the same time, many proprioceptors are stimulated at the end of the range of motion rather than at the midpoint of the range of motion[8,29]. In the case of the shoulder joint, the end of the external rotation is stimulated more often[8]. Therefore, it is possible that proprioceptive abilities were not fully activated during the experiment.

Secondly, the power and proprioceptive conduction pathways are not identical. The processing centers for proprioception are in the posterior part of the posterior central gyrus and paracentral lobule, whereas the motor conduction pathway begins in the anterior part of the precentral gyrus and paracentral lobule[30]. Although the muscular and tendon organ are attached to the muscle, they are essentially two different conduction pathways. The excellent proprioceptive ability of athletes is due to the gradual desensitization of the Golgi tendon organ with prolonged training, increased sensitivity of the musculocutaneous spindle and increased adaptation of peripheral nerves to improve joint position sense[31]. Proprioception does not change with force, and it is thought that proprioception only changes with changes in the muscle spindle and intra-articular proprioceptors[16,32]. Sometimes sports injuries
Table 3 Correlation analysis of strength and proprioception at 60°/s in the shoulder joint of the racket-holding hand in table tennis players

<table>
<thead>
<tr>
<th></th>
<th>Absolute peak torque of external rotation</th>
<th>Relative peak torque of external rotation</th>
<th>Absolute peak torque of internal rotation</th>
<th>Relative peak torque of internal rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>External rotation AE</td>
<td>Spearman -0.055</td>
<td>-0.148</td>
<td>-0.059</td>
<td>-0.178</td>
</tr>
<tr>
<td></td>
<td>P value 0.818</td>
<td>0.533</td>
<td>0.806</td>
<td>0.454</td>
</tr>
<tr>
<td>External rotation CE</td>
<td>Spearman -0.234</td>
<td>-0.315</td>
<td>-0.197</td>
<td>-0.344</td>
</tr>
<tr>
<td></td>
<td>P value 0.321</td>
<td>0.176</td>
<td>0.405</td>
<td>0.137</td>
</tr>
<tr>
<td>External rotation VE</td>
<td>Pearson 0.302</td>
<td>0.136</td>
<td>0.330</td>
<td>0.162</td>
</tr>
<tr>
<td></td>
<td>P value 0.196</td>
<td>0.568</td>
<td>0.155</td>
<td>0.495</td>
</tr>
<tr>
<td>Internal rotation AE</td>
<td>Pearson 0.223</td>
<td>0.018</td>
<td>0.199</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>P value 0.344</td>
<td>0.939</td>
<td>0.399</td>
<td>0.997</td>
</tr>
<tr>
<td>Internal rotation CE</td>
<td>Pearson 0.175</td>
<td>-0.139</td>
<td>0.220</td>
<td>-0.097</td>
</tr>
<tr>
<td></td>
<td>P value 0.459</td>
<td>0.558</td>
<td>0.351</td>
<td>0.683</td>
</tr>
<tr>
<td>Internal rotation VE</td>
<td>Spearman -0.024</td>
<td>0.086</td>
<td>-0.097</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td>P value 0.920</td>
<td>0.719</td>
<td>0.685</td>
<td>0.857</td>
</tr>
</tbody>
</table>

AE: Absolute error; CE: Constant error; VE: Variable error.

Table 4 Correlation analysis of strength and proprioception at 180°/s in the shoulder joint of the racket-holding hand in table tennis players

<table>
<thead>
<tr>
<th></th>
<th>Absolute Peak torque of external rotation</th>
<th>Relative peak torque of external rotation</th>
<th>Absolute peak torque of internal rotation</th>
<th>Relative peak torque of internal rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>External rotation AE</td>
<td>Spearman -0.111</td>
<td>-0.150</td>
<td>-0.204</td>
<td>-0.214</td>
</tr>
<tr>
<td></td>
<td>P value 0.640</td>
<td>0.529</td>
<td>0.388</td>
<td>0.366</td>
</tr>
<tr>
<td>External rotation CE</td>
<td>Spearman -0.113</td>
<td>-0.347</td>
<td>-0.123</td>
<td>-0.420</td>
</tr>
<tr>
<td></td>
<td>P value 0.636</td>
<td>0.133</td>
<td>0.604</td>
<td>0.065</td>
</tr>
<tr>
<td>External rotation VE</td>
<td>Pearson 0.033</td>
<td>0.057</td>
<td>0.040</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td>P value 0.890</td>
<td>0.812</td>
<td>0.868</td>
<td>0.704</td>
</tr>
<tr>
<td>Internal rotation AE</td>
<td>Pearson 0.114</td>
<td>0.082</td>
<td>0.066</td>
<td>0.076</td>
</tr>
<tr>
<td></td>
<td>P value 0.633</td>
<td>0.732</td>
<td>0.782</td>
<td>0.749</td>
</tr>
<tr>
<td>Internal rotation CE</td>
<td>Pearson 0.168</td>
<td>-0.145</td>
<td>0.245</td>
<td>-0.105</td>
</tr>
<tr>
<td></td>
<td>P value 0.478</td>
<td>0.542</td>
<td>0.297</td>
<td>0.660</td>
</tr>
<tr>
<td>Internal rotation VE</td>
<td>Spearman 0.053</td>
<td>0.221</td>
<td>-0.081</td>
<td>0.117</td>
</tr>
<tr>
<td></td>
<td>P value 0.826</td>
<td>0.349</td>
<td>0.736</td>
<td>0.623</td>
</tr>
</tbody>
</table>

AE: Absolute error; CE: Constant error; VE: Variable error.

cause damage not only to the muscle fibers but also to the proprioceptors attached to the muscle, which may explain the simultaneous decrease in proprioception and strength after injury.

Finally, the study population was National Elite Athletes, which may not have the same traits as the healthy population. One study[7] assessed the relationship between strength and proprioception and concluded that strength was associated with power perception in proprioception, while there was no significant relationship with joint position perception. In the methodology of proprioception, it was also stated[33] that tests for different aspects of proprioception are not inherently correlated and that it is one-sided to represent proprioception through one test method. Therefore, this study can only show that there is no significant correlation between positional perception and muscle strength.
Table 5 Correlation analysis of strength and proprioception at 60°/s in the shoulder of non-racket-holding hands of table tennis players

<table>
<thead>
<tr>
<th></th>
<th>Absolute peak torque of external rotation</th>
<th>Relative peak torque of external rotation</th>
<th>Absolute peak torque of internal rotation</th>
<th>Relative peak torque of internal rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>External rotation AE</strong></td>
<td>Pearson -0.044</td>
<td>0.063</td>
<td>-0.077</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.855</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>External rotation CE</strong></td>
<td>Spearman -0.071</td>
<td>0.068</td>
<td>-0.027</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.765</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>External rotation VE</strong></td>
<td>Spearman -0.203</td>
<td>-0.156</td>
<td>-0.138</td>
<td>-0.103</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.391</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Internal rotation AE</strong></td>
<td>Pearson -0.042</td>
<td>0.093</td>
<td>-0.095</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.860</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Internal rotation CE</strong></td>
<td>Pearson 0.084</td>
<td>-0.015</td>
<td>0.118</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.725</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Internal rotation VE</strong></td>
<td>Spearman 0.575</td>
<td>0.477&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.289</td>
<td>0.384</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.103</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*<sup>a</sup>*P < 0.05, muscle strength vs proprioception.

AE: Absolute error; CE: Constant error; VE: Variable error.

Table 6 Correlation analysis of the strength and proprioception at 180°/s in the shoulder joint in the non-racket-holding hand of table tennis players

<table>
<thead>
<tr>
<th></th>
<th>Absolute peak torque of external rotation</th>
<th>Relative peak torque of external rotation</th>
<th>Absolute peak torque of internal rotation</th>
<th>Relative peak torque of internal rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>External rotation AE</strong></td>
<td>Pearson -0.266</td>
<td>0.046</td>
<td>-0.351</td>
<td>-0.025</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.257</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>External rotation CE</strong></td>
<td>Spearman -0.236</td>
<td>-0.099</td>
<td>-0.065</td>
<td>-0.093</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.318</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>External rotation VE</strong></td>
<td>Spearman 0.040</td>
<td>0.083</td>
<td>-0.026</td>
<td>0.136</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.867</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Internal rotation AE</strong></td>
<td>Pearson 0.003</td>
<td>-0.070</td>
<td>-0.087</td>
<td>-0.120</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.990</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Internal rotation CE</strong></td>
<td>Pearson -0.142</td>
<td>0.163</td>
<td>-0.076</td>
<td>0.184</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.551</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Internal rotation VE</strong></td>
<td>Spearman 0.202</td>
<td>0.554&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.226</td>
<td>0.389</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value 0.394</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*<sup>a</sup>*P < 0.05 forces vs proprioception.

AE: Absolute error; CE: Constant error; VE: Variable error.

A study[34] performed bench press strength training on a population with exercise habits and found that after 8 wk of intervention, subjects had increased shoulder joint strength and improved accuracy of position reproduction and attributed the increase in proprioception to their increased strength because of the increased sensitivity of the muscle spindle through strength training, which allows the input of many signals related to proprioception. However, Salles et al[34] interpreted the possibilities only on the basis of experimental results and theoretical situations, and in the above experiments only tested proprioception in the direction of rotation, which is not comprehensive enough to prove a relationship between the two. Similarly, Boarati et al[35] performed similar training and the results did not improve proprioceptive abilities.
The relationship between proprioception and power in the non-racket-holding hand

This study found a positive correlation between the VE of internal rotation and relative peak torque of external rotation in the non-racket-holding hand in both fast and slow speed conditions (see Table 5 and Table 6).

Firstly, the inconsistency between the results of the non-racket-holding hand and those of the racket-holding hand may be explained by the fact that the racket-holding hand, as the dominant measure of the player, has undergone more than a decade of specialized training in table tennis and has undergone adaptive changes in both shoulder joint posture and structural morphology, and as table tennis is a typically asymmetrical sport, the non-racket-holding hand is weaker than the racket-holding hand both in terms of strength and proprioception, and therefore more closely resembles the normal population.

Secondly, the internal rotational VE represents the stability, not the accuracy, of the internal rotational proprioception of the shoulder joint in the non-racket-holding hand. In contrast, when the shoulder joint performs an internal rotation movement, the external rotation muscles coincide with a centrifugal contraction, which better helps the shoulder joint to perform a controlled and stable coordinated movement. Therefore, the two are correlated.

Furthermore, injury occurs when there is an imbalance in shoulder joint muscle strength. Studies have shown[19] that swingers and throwers have much stronger internal rotation muscles than athletes in other sports, and that these sports will lead to more imbalances in rotator cuff musculature, and Ellen et al.[36] found that internal shoulder rotation muscles develop selectively relative to external shoulder rotation muscles (a specific characteristic) and occur at a very young age when they were analyzed for isokinetic muscle strength characteristics. Therefore, the imbalance in shoulder muscle strength can lead to problems in shoulder function and a tendency to cause injury to the rotator cuff muscle groups[37].

The above demonstrates the importance of the external rotation muscles of the shoulder joint—combined with the fact that in table tennis, the shoulder joint performs an inward, forward flexion and inward rotation movement when the player is striking the ball with a forehand loop. As the table tennis player has well-developed chest muscles, it is even more important for the infraspinatus and teres minor muscles to perform centrifugal movements to accurately hit the center of the ball and complete the technical movement.

Comparison of proprioception between the racket-holding hand and non-racket-holding hand

In this study, it was shown that the CE and VE of the racket-holding hand during inward rotation are smaller than those of the non-racket-holding hand, indicating that the directionality, accuracy, and stability of the racket-holding hand are better than those of the non-racket-holding hand during the inward rotation of the shoulder joint. This is clearly the result of years of specific training.

Lage number of repetitive open-chain movements have a significant improvement on the proprioceptive capacity of the shoulder joint[38]. In contrast, the compression to which the joint capsule is subjected during closed-chain training provides proprioceptive stimulation, promoting synergistic activity of the upper shoulder muscles and improving joint stability[39]. There is also super-isokinetic training, which stimulates proprioception at the end of the joint to a greater extent[40], and numerous studies have shown that Plyometric training improves proprioceptive abilities[32,41]. These movement patterns are often found in table tennis technical training and specific physical training.

In summary, these results will assist in the development of a rehabilitation program, which should include both plyometric and proprioceptive training. The above results showed that improvements in muscle strength do not necessarily improve proprioception in the spinal and shoulder joints. Finding a method of training that can train both muscle strength and endurance as well as proprioception can significantly improve performance and save time and medical costs. Upper limb stabilization and plyometric training, which stimulates the body's proprioceptors and trains the body's muscles, may be a recommended exercise therapy. In table tennis, in addition to explosive, multi-ball training program can be enhanced by performing many repetitive movements to improve the stability of the landing point and improve proprioceptive abilities.

### Table 7 Comparison of the Internal and external rotation's absolute error, constant error and variable error of the racket-holding and the non-racket-holding hand

<table>
<thead>
<tr>
<th></th>
<th>External rotation</th>
<th>Internal rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AE</td>
<td>CE</td>
</tr>
<tr>
<td>Z value</td>
<td>-0.947</td>
<td>-1.244</td>
</tr>
<tr>
<td>P value</td>
<td>0.355</td>
<td>0.221</td>
</tr>
</tbody>
</table>

*a P < 0.01, the internal rotation constant error, variable error of the racket-holding hand vs that of the non-racket-holding hand.

AE: Absolute error; CE: Constant error; VE: Variable error.
CONCLUSION

There is no correlation between muscle strength and proprioceptive function in the internal and external rotation of the shoulder in elite Chinese male table tennis players. These results may be useful for interventions for shoulder injuries and for the inclusion of proprioceptive training in rehabilitation programs.

ARTICLE HIGHLIGHTS

Research background
With the constant change of the rules of table tennis, more and more table tennis players emerge, which puts forward higher requirements for the awareness of landing point and the coordination of hitting. The sense of motion and position in proprioception is of great significance to the control of limbs and the judgment of landing points, so the proprioception of table tennis players is evaluated and tested.

Research motivation
Shoulders are the most injured part in table tennis players because the joint has multiple roles in transmitting power and striking the center of the ball during the stroke. Proprioception is strongly correlated with high level of athletic performance. It is customary to assume that there is a correlation between proprioception and muscle strength, and therefore, proprioceptive assessment and rehabilitation are often neglected.

Research objectives
This study was performed to investigate the correlation between isokinetic muscle strength and proprioception in the internal and external rotation muscle groups of elite Chinese male table tennis players, to provide reference for physical training and rehabilitation.

Research methods
The subjects were elite players from the Chinese National Table Tennis Team. All of them had > 10 years’ training experience and had participated in major competitions such as the National Games and World Youth Championships. IsoMed 2000 was used to test the peak torque of internal and external rotation isokinetic concentric contraction of the athletes’ bilateral shoulder joints at low speed (60°/s) and high speed (180°/s). IsoMed 2000 was used to conduct the Joint Position Reproduction test to evaluate the athletes’ proprioceptive capacity at low speed (60°/s) and high speed (180°/s).

Research results
At slow speed and fast speed, there is no direct linear relationship between hand strength and proprioceptive correlation analysis. At slow speed and fast speed, there is a moderate positive correlation except for internal spin variable error (VE) and external spin relative peak torque. The internal rotation constant errors (CE) and VE were 1.06 ± 3.99 and 2.94 ± 2.16 for handgrip, and -3.36 ± 2.39 and 1.22 ± 0.93 for non-handgrip. The internal rotation CE and VE of handgrip were significantly lower than those of non-handgrip (P < 0.01).

Research conclusions
There was no correlation between muscle strength and proprioceptive function in the internal and external rotation of the shoulder of the racket-holding hand in elite Chinese male table tennis players. These results may be useful for interventions for shoulder injuries and for the inclusion of proprioceptive training in rehabilitation programs.

Research perspectives
Proprioception is a complex concept, and this study only explored the sense of position and movement, but did not study the sense of speed and force. It also links proprioception to specific tests, such as hitting points, which can help improve performance.

FOOTNOTES

Author contributions: Shang XD and Zhang EM contributed equally to this work; both Shang XD and Qian JH are the corresponding authors; Shang XD, Zhang EM, Chen ZL, Zhang L and Qian JH designed the research study; Shang XD, Zhang EM, and Qian JH performed the research; Shang XD, Zhang EM, Chen ZL and Zhang L analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.
Institutional review board statement: The study was reviewed and approved by the Exercise Science Experiment of Beijing Sport University Institutional Review Board (Approval No.2021075H).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

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Country/Territory of origin: China

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S-Editor: Wang JL
L-Editor: A
P-Editor: Wang JL

REFERENCES


33. Li L, Ji ZQ, Li YX, Liu WT. [Correlation between Joint Position Sense Reproduce Test, the Threshold of Detection of Movement Test and Force Sense Reproduce Test]. *Tianjin Ti Yu xue yuan xue bao* 2016; 31: 36-40 [DOI: 10.13297/j.cnki.issn1005-0000.2016.01.007]


Clinical value of contrast-enhanced ultrasound in early diagnosis of small hepatocellular carcinoma (≤ 2 cm)

Qi Mei, Mei Yu, Qiong Chen

BACKGROUND
Hepatocellular carcinoma (HCC) is the most common type of primary liver malignancy. Contrast-enhanced ultrasound (CEUS) uses contrast microbubbles during ultrasound, allowing the detection and characterization of malignant focal liver lesions with much higher diagnostic accuracy than conventional ultrasound; however, there are few reports focusing on the pattern of enhancement of CEUS for the diagnosis of HCC smaller than 2 cm.

AIM
To investigate the clinical value of CEUS in the early detection of small HCC with high risk factors.

METHODS
A total of 395 patients with 632 nodules at high risk of HCC, who underwent regular follow-up at Xuhui Dahua Hospital from January 2007 to December 2021, were retrospectively examined. Conventional ultrasonography combined with CEUS was adopted to analyze the echo, size, location, and enhancement characteristics of benign and malignant nodules, as well as the enhancement methods for HCC with different diameters.

RESULTS
The follow-up rate and duration were 92.15% (364/395) and 51.28 ± 45.09 mo, respectively. Conventional ultrasonography combined with CEUS revealed 65 (11.80%) nodules with a follow-up diagnosis of HCC, 19 (3.45%) dysplastic nodules, and 467 (84.75%) benign cirrhotic hyperplastic nodules. Among 65 cases of confirmed HCC, 40 (61.54%) were transformed from hypoechoic nodules, 9 (13.85%) from hyperechoic nodules, and the remaining 16 (24.62%) from isoechoic nodules.

Abstract

Backgound
Hepatocellular carcinoma (HCC) is the most common type of primary liver malignancy. Contrast-enhanced ultrasound (CEUS) uses contrast microbubbles during ultrasound, allowing the detection and characterization of malignant focal liver lesions with much higher diagnostic accuracy than conventional ultrasound; however, there are few reports focusing on the pattern of enhancement of CEUS for the diagnosis of HCC smaller than 2 cm.

Aim
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Methods
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Results
The follow-up rate and duration were 92.15% (364/395) and 51.28 ± 45.09 mo, respectively. Conventional ultrasonography combined with CEUS revealed 65 (11.80%) nodules with a follow-up diagnosis of HCC, 19 (3.45%) dysplastic nodules, and 467 (84.75%) benign cirrhotic hyperplastic nodules. Among 65 cases of confirmed HCC, 40 (61.54%) were transformed from hypoechoic nodules, 9 (13.85%) from hyperechoic nodules, and the remaining 16 (24.62%) from isoechoic nodules.
nodules. Significant differences in CEUS characteristics were found among cirrhotic nodules, dysplastic nodules, and HCC nodules at each phase. Significant differences in the enhancement mode were observed between nodules ≤ 1 cm and those 1–2 cm. The smaller the HCC nodule, the later the contrast agent began to flush and the longer the duration of contrast enhancement.

**CONCLUSION**

Conventional ultrasonography combined with CEUS could identify small HCC and help monitor patients with an early diagnosis of HCC. Significant differences in the enhancement mode are noted between nodules ≤ 1 cm and those 1–2 cm.

**Key Words:** Carcinoma; Hepatocellular; Contrast-enhanced ultrasonography; Diagnostic imaging

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**Core Tip:** Conventional ultrasonography combined with contrast-enhanced ultrasound is a feasible way to identify small hepatocellular carcinoma (HCC) and help monitor patients with small HCC. There are significant differences between the liver nodules ≤ 1 cm and those in the range 1-2 cm regarding enhancement mode.

**INTRODUCTION**

Liver cancer is the sixth most common cancer worldwide, but the third most common cause of cancer-related death[1]. Hepatocellular carcinoma (HCC) is the most common type of primary liver malignancy. Approximately 548000 people are diagnosed with HCC every year, and almost as many people die as a result of it[2]. Developing countries have a two to three times higher incidence of HCC compared with Western countries[3]. It is estimated that the incidence of HCC will continue to increase until 2030[4].

Imaging, involving multiphase computed tomography (CT) or magnetic resonance imaging (MRI), forms the basis for the diagnosis of HCC[5]. The development and progression of HCC are accompanied by a series of changes in hemodynamics in the lesion. During the transformation of a cirrhotic nodule to a dysplastic nodule and small HCC, the blood supply of the nutrient arteries in the nodule gradually increases, while that of the original portal vein gradually decreases. Ultrasound is a safe, commonly available, and cost-effective tool for screening patients with cirrhosis for HCC, but its diagnostic use is limited by its low specificity due to the variable appearances of HCC. The diagnostic accuracy of conventional ultrasonography for hepatic space-occupying lesions is only 53%–77%[6]. Contrast-enhanced ultrasound (CEUS) uses contrast microbubbles during ultrasound, allowing the detection and characterization of malignant focal liver lesions with much higher diagnostic accuracy[7]. The main advantage of CEUS is its ability to display microcirculatory blood perfusion of tissues in real time. The differences in the blood perfusion of benign and malignant tumors allow sonographers to make a qualitative and quantitative diagnosis[8]. It greatly increases the detection rate and diagnostic accuracy of early-stage tumors and satellite lesions of malignant tumors[9].

The diagnosis of small HCC relies solely on imaging because patients usually have no clinical signs[10]. However, these small nodules rarely display the radiological hallmarks of HCC[11]. Delaying diagnosis until the development of < 2 cm nodules results in increased treatment failure or recurrence[12]. The use of CEUS to monitor and diagnose small HCC may improve patient outcomes.

We hypothesized that CEUS would be safe and effective in detecting small HCC. Therefore, the present study was conducted to investigate the clinical value of CEUS in the early detection of small HCC in patients at high risk of HCC. We analyzed the data of regular conventional color Doppler ultrasonography, follow-up, and CEUS of the liver performed in patients at high risk for HCC in our department followed for more than 10 years.
MATERIALS AND METHODS

Participants
From January 2007 to December 2021, the clinical data of patients at high risk of HCC who underwent regular follow-up at Xuhui Dahua Hospital were retrospectively collected. The inclusion criteria were as follows: (1) Patients with chronic liver disease and those with cirrhosis diagnosed by clinical and related imaging examinations; (2) Patients with cirrhosis complicated by intrahepatic space-occupying lesions, but undetermined nature of the lesions, or increase in one of the combined indicators of HCC [alpha-fetoprotein (AFP) or the new HCC marker glypican-3], but imaging examination showing no space-occupying lesions; (3) Family history of HCC; and (4) Status post HCC surgery. The exclusion criteria were as follows: (1) Hepatic tumor greater than 2 cm in diameter, or patients with advanced tumors complicated by a portal vein tumor thrombus; and (2) Patients with metastatic liver cancer. This study was approved by the Dahua Hospital of Xuhui District Institutional Review Board (No. 201607). The patients gave consent for inclusion in the study.

Diagnostic criteria
The whole dynamic process of liver CEUS included arterial phase (15–30 s), portal phase (31–120 s), and delayed phase (121–360 s). A differential diagnosis was performed based on the hemodynamic characteristics of the intrahepatic nodules on dynamic CEUS depending on the time of wash-in and wash-out. According to the American College of Radiology (ACR) CEUS Liver Imaging Reporting and Data System (CEUS LI-RADS), the CEUS features of HCC included homogeneous or inhomogeneous hyperechoic enhancement in the arterial phase and hypoechogenic enhancement in the portal and delayed phases, which was called the "fast-in and fast-out" type and was a typical enhancement pattern of HCC.[13,14] Specifically, if CEUS showed rapid wash-in and no significant wash-out in the portal and delayed phases, namely, a "fast-in and isochronous-out" type, it was considered an atypical enhancement pattern of HCC (mostly manifestation patterns of small HCC). If CEUS showed that the lesion area had slower wash-in, and the portal and delayed phases showed isoechogenic enhancement and wash-out isochronously as with the liver parenchyma, namely, the "slow-in and isochronous-out" type, it suggested a dysplastic nodule. If CEUS showed isochronous enhancement for the intrahepatic lesion area and the peripheral liver parenchyma and the portal and delayed phases showed isoechogenic enhancement and wash-out isochronously as with the liver parenchyma, it suggested a benign liver nodule.

All patients were clinically diagnosed with small HCC according to the HCC treatment guidelines issued by the European Association for the Study of the Liver. Common imaging tests included four-phase multidetector CT and dynamic contrast-enhanced MRI. Clinical diagnosis of small HCC was comprehensively based on the patient’s history of chronic liver disease, AFP (> 400 μg/L for 1 mo or > 200 μg/L for over 2 mo), and typical HCC manifestations revealed by imaging examinations (hypervascular liver lesions in the arterial phase with washout in the portal veins or in the delayed phase).[15] Patients with a high suspicion of HCC were treated by puncture and then surgery.

Examination method
Color ultrasound instruments (Siemens Sequoia 512 and Siemens S2000, Siemens Ltd., Munich, Germany; Philips iU22, Royal Dutch Philips Electronics Ltd., Amsterdam, Netherlands, and LOGIQ E9, General Electric Co., Fairfield, Connecticut, United States) were used with an abdominal convex array probe, at a frequency of 1–5 MHz. The contrast agent was SonoVue containing 59 mg sulfur hexafluoride gas, and the microbubble suspension was prepared using 5 mL of 0.9% NaCl solution. According to the weight of each patient, a microbubble suspension of 2 mL/50 kg was taken for Siemens Sequoia 512 and S2000 ultrasound instruments, and 0.1 mL was added for each additional 5 kg. For Philips iU22 and GE LOGIQ E9, 1 mL/50 kg of the suspension was used and 0.1 mL was added for each additional 5 kg. The microbubble suspension was added via bolus injection through the peripheral vein, and 5 mL of 0.9% NaCl solution was intravenously injected immediately. The CEUS information was stored in the form of real-time dynamic video and qualitative and quantitative analyses of the contrast enhancement mode were conducted.

CEUS was performed by associate chief physicians and reviewed by physicians with the same qualification or superior physicians.

Statistical analysis
Statistical analyses were performed using SPSS software V. 22.0 (IBM Corp., Armonk, NY, United States). Categorical data are presented as n (%). Continuous data with a normal distribution are presented as the mean ± SD. Measurement data in the two groups were compared using a two-sample unpaired-sample t test. Categorical data were compared using the chi-square test. Simple logistic regression was used to analyze and weigh various ultrasound indicators and overall scores in predicting the odds ratio of HCC. P < 0.05 indicated a statistically significant difference.
RESULTS

Baseline characteristics

A total of 395 patients were enrolled in the 14 years of follow-up, including 230 men and 165 women. Their age range was 11–85 years, with a mean of 54.67 ± 12.84 years. In these patients, 632 nodules were detected. The follow-up rate was 92.15% (364/395), and the rate of loss to follow-up was 7.85% (31/395); 14 died of decompensated cirrhosis or other cardiovascular diseases, and 17 withdrew from the chronic disease management group. A total of 551 nodules in 364 patients were selected for follow-up. During the regular follow-up every 3 mo, according to CEUS, 65 (11.80%) were diagnosed with HCC, 19 (3.45%) with dysplastic nodules, and 467 (84.75%) with benign cirrhotic hyperplastic nodules (Figure 1 and Table 1). In 65 patients diagnosed with HCC based on CEUS, 55 (84.6%) were pathologically confirmed by further needle biopsy. Of the 93 patients who underwent surgery and needle biopsy, 1 had missed diagnosis (1 patient had 2 HCC nodules in the liver, but only 1 was found by CEUS). This might be related to the scanning section selected by physicians or the blind area of the scanning section of the liver using CEUS. No significant error was found between the HCC nodule size in surgical results and that found using CEUS (error ≤ 5 mm).

Ultrasound and CEUS characteristics of the nodules

The ultrasound characteristics of the nodules classified into HCC and non-HCC groups are shown in Table 2. Significant differences were found between the groups, except for nodule location. A total of 40 nodules (61.54%) were transformed from hypoechoic nodules to HCC, 9 (13.85%) from hyperechoic nodules to HCC, and 467 (84.75%) from benign cirrhotic hyperplastic nodules to HCC.
Table 1 Baseline characteristics of patients grouped according to classification of their liver nodules

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients (n = 364)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCC (n = 65)</td>
<td>Non-HCC (n = 299)</td>
</tr>
<tr>
<td>Age (yr), mean ± SD</td>
<td>49.86 ± 0.84</td>
<td>60.40 ± 1.72</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>45 (69.23)</td>
<td>218 (72.90)</td>
</tr>
<tr>
<td>Family history of HCC, n (%)</td>
<td>8 (12.31)</td>
<td>11 (3.67)</td>
</tr>
<tr>
<td>BMI (kg/m^2), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 28</td>
<td>4 (6.15)</td>
<td>28 (9.36)</td>
</tr>
<tr>
<td>≤ 28</td>
<td>61 (93.85)</td>
<td>211 (90.94)</td>
</tr>
<tr>
<td>HBV, n (%)</td>
<td>65 (100)</td>
<td>219 (73.24)</td>
</tr>
<tr>
<td>HCV, n (%)</td>
<td>2 (3.08)</td>
<td>24 (8.03)</td>
</tr>
<tr>
<td>Alcohol cirrhosis, n (%)</td>
<td>2 (3.08)</td>
<td>5 (1.67)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>8 (12.3)</td>
<td>46 (15.38)</td>
</tr>
</tbody>
</table>

HCC: Hepatocellular carcinoma; BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NS: No significant.

Table 2 Comparison of ultrasonographic characteristics between hepatocellular carcinoma and non-hepatocellular carcinoma nodules

<table>
<thead>
<tr>
<th>Category</th>
<th>Nodules (n = 551)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCC (n = 65)</td>
<td>Non-HCC (n = 486)</td>
</tr>
<tr>
<td>Ultrasonographic characteristics, n (%)</td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Hyperecho</td>
<td>13 (20)</td>
<td>175 (36.01)</td>
</tr>
<tr>
<td>Isoecho</td>
<td>5 (7.69)</td>
<td>12 (2.47)</td>
</tr>
<tr>
<td>Hypoecho</td>
<td>47 (72.31)</td>
<td>299 (61.52)</td>
</tr>
<tr>
<td>Nodule size (mm)</td>
<td>14.6 ± 0.48</td>
<td>12.2 ± 10.27</td>
</tr>
<tr>
<td>Location, n (%)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Left liver</td>
<td>9 (13.85)</td>
<td>77 (15.84)</td>
</tr>
<tr>
<td>Right liver</td>
<td>56 (86.15)</td>
<td>409 (84.16)</td>
</tr>
</tbody>
</table>

HCC: Hepatocellular carcinoma; NS: No significant.

Comparison of CEUS in different-sized HCC nodules

As shown in Table 4, a comparison of CEUS findings according to the size of the HCC nodules revealed significant differences between the nodules ≤ 1 cm and those 1–2 cm in enhancement time and pattern (P < 0.05). Figure 2 shows that the HCC nodule size negatively correlated with the start time of wash-out of the contrast agent, with a correlation coefficient (r) of –0.386. The smaller the HCC nodule, the later the contrast agent began to wash out (Figures 3 and 4). The HCC nodule size negatively correlated with the duration of enhancement of the contrast agent (r = –0.349). The smaller the HCC nodule, the longer the duration of enhancement of the contrast agent.

DISCUSSION

This study aimed to diagnose patients with chronic liver disease using convenient, safe, inexpensive, and real-time dynamic ultrasonic examinations. Conventional ultrasound and CEUS were used for screening, grouping, and monitoring of patients with chronic liver disease, so as to achieve an early diagnosis of small HCC. A total of 65 patients with HCC were diagnosed in early monitoring during the
Table 3: Contrast-enhanced ultrasound findings in cirrhotic nodules, dysplastic nodules, and hepatocellular carcinoma

<table>
<thead>
<tr>
<th>CEUS characteristic, n (%)</th>
<th>Nodules (n = 551)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CN (n = 467)</td>
<td>DN (n = 19)</td>
</tr>
<tr>
<td>Arterial phase</td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Hyperecho</td>
<td>0</td>
<td>1 (5.26)</td>
</tr>
<tr>
<td>Isoecho</td>
<td>438 (93.79)</td>
<td>8 (42.11)</td>
</tr>
<tr>
<td>Hypoecho</td>
<td>29 (6.21)</td>
<td>10 (52.63)</td>
</tr>
<tr>
<td>Portal phase</td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Hyperecho</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Isoecho</td>
<td>464 (99.36)</td>
<td>17 (89.47)</td>
</tr>
<tr>
<td>Hypoecho</td>
<td>3 (0.64)</td>
<td>2 (10.53)</td>
</tr>
<tr>
<td>Delayed phase</td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Hyperecho</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Isoecho</td>
<td>464 (99.36)</td>
<td>17 (89.47)</td>
</tr>
<tr>
<td>Hypoecho</td>
<td>3 (0.64)</td>
<td>2 (10.53)</td>
</tr>
</tbody>
</table>

CEUS: Contrast-enhanced ultrasound; CN: Cirrhotic nodule; DN: Dysplasia; HCC: Hepatocellular carcinoma.

Table 4: Contrast-enhanced ultrasound findings in small hepatocellular carcinoma of different sizes

<table>
<thead>
<tr>
<th>Category</th>
<th>Nodule size</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 1 cm</td>
<td>1-2 cm</td>
</tr>
<tr>
<td>No.</td>
<td>13</td>
<td>52</td>
</tr>
<tr>
<td>Type of echo, n (%)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Hyperecho</td>
<td>1 (7.69)</td>
<td>8 (15.38)</td>
</tr>
<tr>
<td>Isoecho</td>
<td>2 (15.38)</td>
<td>14 (26.92)</td>
</tr>
<tr>
<td>Hypoecho</td>
<td>10 (76.92)</td>
<td>30 (57.69)</td>
</tr>
<tr>
<td>Enhancement time (s), mean ± SD</td>
<td>15.12 ± 1.44</td>
<td>19.90 ± 0.61</td>
</tr>
<tr>
<td>Wash-out time (s), mean ± SD</td>
<td>115.20 ± 10.25</td>
<td>80.13 ± 13.18</td>
</tr>
<tr>
<td>Arterial phase (0-30 s), n (%)</td>
<td>0</td>
<td>1 (1.92%)</td>
</tr>
<tr>
<td>Portal phase (31-120 s), n (%)</td>
<td>4 (30.77)</td>
<td>28 (53.85)</td>
</tr>
<tr>
<td>Delayed phase (121-360 s), n (%)</td>
<td>1 (7.69)</td>
<td>4 (7.69)</td>
</tr>
<tr>
<td>&gt; 360 s, n (%)</td>
<td>8 (61.54)</td>
<td>19 (36.54)</td>
</tr>
<tr>
<td>CEUS pattern, n (%)</td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Fast-in and fast-out</td>
<td>5 (38.46)</td>
<td>33 (63.46)</td>
</tr>
<tr>
<td>Fast-in and isochronous-out</td>
<td>8 (61.54)</td>
<td>19 (36.54)</td>
</tr>
</tbody>
</table>

CEUS: Contrast-enhanced ultrasound; NS: No significant.

11-year study involving 395 patients with chronic liver disease in different stages. The confirmation rate was 99.6% (64/65), with one missed diagnosis because the patient had two HCC nodules on the liver and the second nodule was found on a preoperative MRI scan. The use of CEUS in this study allowed stratification of the small hepatic nodules into HCC and non-HCC groups to identify patients in need of comprehensive prevention and treatment.

In this study, early and regular evaluation by CEUS revealed hyperechoic enhancement in the arterial phase of the cirrhotic nodules. HCC could be confirmed regardless of whether it had a "fast-in and fast-out" or "fast-in and isochronous-out" pattern. A change in the contrast enhancement mode suggested
Figure 3 Representative images of contrast-enhanced ultrasound and pathological specimen from a 45-year-old woman. A: A hyperechoic nodule (arrow) shown in the left lobe of the liver in the arterial phase (19 s); B: The same nodule (arrow) was visualized in the delayed phase (125 s); C: The pathological specimen after surgery resection displayed a tumor about 10 mm in diameter. Enhancement during time: 160 s.

Figure 4 Representative images of contrast-enhanced ultrasound and pathological specimen from an 11-year-old child. A: A hyperechoic nodule (arrow) shown in the right lobe of the liver in the arterial phase (18 s); B: The same nodule was visualized in the delayed phase (128 s); C: The pathological specimen after surgery resection displayed a tumor (wide diameter 10 mm, long diameter 18 mm). Enhancement during time: 130 s.

pathological changes in the nodules. The development of the ACR CEUS LI-RADS has been welcomed for its standardization of CEUS information, allowing for a more accurate diagnosis of hepatic nodules [16]. The LI-RADS uses the size of a lesion, the type and degree of arterial phase enhancement, the presence of wash-out, and the timing and degree of wash-out as the major features used for categorizing CEUS images [13]. These features were also significant in the present study in differentiating between cirrhotic nodules, dysplastic nodules, and HCC.

CEUS for small nodules is important for patients at risk of HCC because the diagnosis of a single small HCC comes with a good prognosis and provides a potential for cure [17]. This study showed a high rate of diagnosis of small HCCs, which were all later confirmed to be HCCs. These results compared well with the findings of other studies that aimed to distinguish HCC from benign nodules when they were smaller than 2 cm. The use of gadoxetic acid–enhanced and diffusion-weighted MRI resulted in a sensitivity and accuracy of 91% and 89%, respectively [18]. Another study using LI-RADS with CT achieved a sensitivity and specificity of 72.7% and 90%, respectively [19]. However, one study used CEUS to identify hypervascularity in 190 nodules (95.5%) of 199 histologically confirmed HCC nodules [20]. The advantage of CEUS over other methods with similar results is that it is a modification of the standard ultrasound screening. However, the technique does have some limitations. As shown by the missed diagnosis of one HCC in a patient who already had one HCC, the ultrasonic examination of the liver showed blind areas and interference by gas, or the ribs might result in a missed diagnosis. To address this, it is necessary to select different sections and change positions to observe various sections of the liver. CEUS is also a technique that requires experience, proficiency in section examinations, and understanding of nodules. Insufficient proficiency or understanding may lead to missed diagnosis or misdiagnosis.

In this study, patients with a high suspicion of HCC, such as LR-3, LR-4, and LR-5 according to CEUS LI-RADS, were treated by puncture and then surgery. Generally, the biopsy was performed by physicians in Ultrasound and Intervention Department. Once HCC was confirmed by pathological
methods, the patients should undergo surgery. In order to reduce the possibility of tumor implantation and recurrence, the resection margin should be obviously larger than the diameter of tumor nodules (Figures 3 and 4). Many studies have explored the CEUS images of HCC larger than 20 mm[15,20,21], but comparative studies between HCC nodules ≤ 1 cm and those 1–2 cm are few. However, this study compared the enhancement mode of CEUS for small HCC nodules ≤ 2 cm of different sizes. The results showed that the smaller the HCC nodule, the longer the duration of enhancement of the contrast agent. This might be related to the differentiation of HCC and the blood supply of the hepatic artery and portal vein for HCC. The mechanism of why this enhancement mode is formed needs further exploration.

The study had some limitations. The patients were enrolled from one medical center, and hence the number of small HCC was lower. A larger study from more centers would provide more evidence for these results. No direct comparison with alternative MRI or CT methods was found. So, we cannot directly infer that CEUS is superior to CT or MRI for the diagnosis of small HCC.

CONCLUSION

Conventional ultrasonography combined with CEUS could identify small HCC and help monitor patients with early diagnosis of HCC. Significant differences are found in the enhancement of cirrhotic nodule, dysplasia, and HCC using CEUS, and also between the HCC nodules ≤ 1 cm and those 1–2 cm in the enhancement mode.

ARTICLE HIGHLIGHTS

Research background
Contrast-enhanced ultrasound (CEUS) is challenging in the diagnosis of small hepatocellular carcinoma (HCC) with a diameter of less than 2 cm.

Research motivation
Many studies have explored the CEUS images of HCC larger than 20 mm, but comparative studies between HCC nodules ≤ 1 cm and those 1–2 cm are rare. However, this study compared the enhancement mode of CEUS for small HCC nodules ≤ 2 cm of different sizes.

Research objectives
To investigate the clinical value of CEUS in the early detection of small HCC with high risk factors, especially to compare the enhancement mode of CEUS for small HCC nodules ≤ 2 cm of different sizes.

Research methods
Conventional ultrasonography combined with CEUS was adopted to analyze the echo, size, location, and enhancement characteristics of benign and malignant nodules, as well as the enhancement methods for HCC with different diameters.

Research results
Conventional ultrasonography combined with CEUS revealed 65 (11.80%) nodules with a follow-up diagnosis of HCC, 19 (3.45%) dysplastic nodules, and 467 (84.75%) benign cirrhotic hyperplastic nodules. There were 40 cases (61.54%) of HCC transformed from hypoechoic nodules, 9 (13.85%) from hyperechoic nodules, and the remaining 16 (24.62%) from isoechoic nodules. Significant differences in CEUS characteristics were found among cirrhotic nodules, dysplastic nodules, and HCC nodules in each phase. Significant differences in the enhancement mode were observed between nodules ≤ 1 cm and those 1–2 cm.

Research conclusions
Conventional ultrasonography combined with CEUS could identify small HCCs and help monitor patients with an early diagnosis of HCC. Significant differences in the enhancement mode were noted between nodules ≤ 1 cm and those between 1–2 cm. The smaller the HCC nodule, the later the contrast agent began to flush and the longer the duration of contrast enhancement.

Research perspectives
Small HCC ultrasound imaging enhancement pattern compared with other medical imaging enhancement pattern is the research direction in the future.
FOOTNOTES

Author contributions: Mei Q and Yu M contributed equally to this study; Chen Q designed the research study; Yu M performed the research; Yu M contributed new reagents and analytic tools; Mei Q analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

Supported by: National Natural Science Foundation of China, No. 81571675; Academic Experience and Research Workshop Construction Project of Shanghai Famous TCM Doctors, No. JCZYGZS-008; and Clinical Study on Control and Clearance of Hepatitis B Surface Antigen by Traditional Chinese Medicine, No. 1304190290A.

Institutional review board statement: The study was reviewed and approved by the Dahua Hospital of Xuhui District Institutional Review Board (No. 201607).

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: Dr. Chen reports non-financial support from National Natural Science Foundation of China, personal fees from the Academic Experience and Research Workshop Construction Project of Shanghai Famous TCM Doctors, personal fees from the Clinical Study on Control and Clearance of Hepatitis B Surface Antigen by Traditional Chinese Medicine, during the conduct of the study.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at cq1444@sina.com.

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S-Editor: Fan JR
L-Editor: Wang TQ
P-Editor: Fan JR

REFERENCES

Mei Q et al. CEUS for diagnosis of small HCC


19 Abd Alkhalik Basha M, Abd El Aziz El Sammak D, El Sammak AA. Diagnostic efficacy of the Liver Imaging-Reporting and Data System (LI-RADS) with CT imaging in categorising small nodules (10-20 mm) detected in the cirrhotic liver at screening ultrasound. *Clin Radiol* 2017; 72: 901.e1-901.e11 [PMID: 28673446 DOI: 10.1016/j.crad.2017.05.019]


Identification of predictive factors for post-transarterial chemoembolization liver failure in hepatocellular carcinoma patients: A retrospective study

Min Yuan, Tian-You Chen, Xiao-Rong Chen, Yun-Fei Lu, Jia Shi, Wen-Si Zhang, Chen Ye, Bo-Zong Tang, Zong-Guo Yang

BACKGROUND
Post-transarterial chemoembolization (TACE) liver failure occurs frequently in hepatocellular carcinoma (HCC) patients. The identification of predictors for post-TACE liver failure is of great importance for clinical decision-making in this population.

AIM
To investigate the occurrence rate and predictive factors of post-TACE liver failure in this retrospective study to provide clues for decision-making regarding TACE procedures in HCC patients.

METHODS
The clinical records of HCC patients treated with TACE therapy were reviewed. Baseline clinical characteristics and laboratory parameters of these patients were extracted. Logistic models were used to identify candidates to predict post-TACE liver failure.

RESULTS
A total of 199 HCC patients were enrolled in this study, and 70 patients (35.2%)
developed post-TACE liver failure. Univariate and multivariate logistic models indicated that microspheres plus gelatin embolization and main tumor size > 5 cm were risk predictors for post-TACE liver failure [odds ratio (OR): 4.4, 95% confidence interval (CI): 1.2-16.3, \( P = 0.027 \); OR: 2.3, 95% CI: 1.05-5.3, \( P = 0.039 \), respectively]. Conversely, HCC patients who underwent tumor resection surgery before the TACE procedure had a lower risk for post-TACE liver failure (OR: 0.4, 95% CI: 0.2-0.95, \( P = 0.039 \)).

**CONCLUSION**

Microspheres plus gelatin embolization and main tumor size might be risk factors for post-TACE liver failure in HCC patients, while prior tumor resection could be a favorable factor reducing the risk of post-TACE liver failure.

**Key Words:** Transarterial chemoembolization; Liver failure; Hepatocellular carcinoma; Embolization; Tumor size

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**Core Tip:** Post-transarterial chemoembolization (TACE) liver failure occurs frequently in hepatocellular carcinoma (HCC) patients. Unfortunately, the incidence and risk factors for post-TACE liver failure are inconsistent worldwide. This study addressed the occurrence rate and potential risk factors for post-TACE liver failure according to a single-center retrospective report. The results of this study should attract the attention of relevant medical practitioners and provide predictive clues for the precise interventional treatment of HCC patients.

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**INTRODUCTION**

Hepatocellular carcinoma (HCC) is predicted to be one of the most lethal cancers worldwide[1,2]. According to the Surveillance, Epidemiology, and End Results (SEER) registration agency project research, the incidence of HCC will continue to increase by 2030[3]. In addition, the annual mortality rate associated with liver cancer has increased significantly in the past two decades[4], and the survival of HCC patients with intermediate-advanced tumor stages has progressively decreased[5,6,7]. Currently, transarterial chemoembolization (TACE) is recommended as a first-line treatment strategy for patients with unresectable HCC[1,5]. Although the benefits of the TACE procedure have been demonstrated[1,6], there is still a lack of reliable evidence showing that TACE has a clear superiority over bland embolization. Even worse, the incidence of severe adverse events significantly increased after TACE[7]. Thus, post-TACE liver failure that most commonly causes death after TACE should not be ignored[5].

Post-TACE liver failure is one of the most lethal complications in HCC patients. In South Korea, 12% to 15% of patients treated with TACE developed acute liver failure within 14 d[8,9]. A prospective study in Hong Kong showed that the incidence of liver failure after TACE was approximately 20%[10]. In India, the incidence of post-TACE liver failure was 23.8% to 28.8% in HCC patients[11,12]. In a randomized trial in Europe, the results illustrated that approximately 60% of patients had liver failure after TACE more than once[13]. According to the results of the meta-analysis, 7.5% (range 0-48.6%) of HCC patients developed liver failure after TACE. The mortality rate associated with TACE treatment is 2.4% (0-9.5%), which is mainly due to liver failure after TACE[9]. In the first year after TACE treatment, more than 90% of post-TACE liver failure cases died. Therefore, liver failure after TACE is an independent risk factor for the lower survival rate of liver cancer patients[8]. Hence, identifying the risk factors that can predict the occurrence of post-TACE liver failure in HCC patients is of great importance[8].

This retrospective study aimed to assess the potential clinical characteristics and laboratory parameters that could be predictors for post-TACE liver failure, in the hope that our findings might be helpful for the early detection and early intervention of post-TACE liver failure in HCC patients.
MATERIALS AND METHODS

Ethics statement
The study protocol was reviewed and approved by the Ethics Committee, Shanghai Public Health Clinical Center, Fudan University (approval No. 2021-S062-01). Written informed consent was waived for this retrospective study.

Patients
The diagnosis of HCC was determined by pathology or according to radiological standards, according to the “Guidelines for the Diagnosis and Treatment of Primary Liver Cancer in China (2019 edition)”. Two imaging approaches, including computed tomography (CT) or magnetic resonance imaging (MRI) to show arterial enhancement quality or an imaging study (CT or MRI) showing arterial enhancement quality and alpha-fetoprotein (AFP) level greater than 400 ng/mL were used[14]. HCC patients undergoing TACE as part of standard therapy between January 2019 and May 2020 in Shanghai Public Health Clinical Center, Fudan University, were included. The inclusion criteria were age ≥ 18 years and Child-Turcotte-Pugh (CTP) stage A and B. HCC patients who were pregnant or CTP stage C or had uncontrolled encephalopathy, underlying kidney failure, acute coronary syndromes or valvular heart diseases were excluded from our study.

Treatment procedure for TACE
The China Liver Cancer Staging was used to determine the necessity for the TACE procedure[14]. All HCC patients fasted overnight. The femoral artery was catheterized with a 5F sheath under local anesthesia. A thorough angiographic examination depicting the anatomy of the hepatic artery, tumor blush, feeding arteries, and arteriovenous shunts was performed. Contrast-enhanced CT or MRI and indirect portography were performed during angiography to ensure stable flow in the portal vein. A microcatheter for the injection of chemotherapeutic drugs and embolic agents was placed selectively in the segment arteries or superselectively in the tumor supplying arteries, which feed the HCC lesions. Two types of microspheres, 300-500 μm and 500-700 μm, were used. Combined embolization of microspheres and gelatin sponge particles was applied for patients with larger tumor sizes (diameter > 5 cm). The volume of lipiodol ranged from 4 to 30 mL, pirarubicin ranged from 0 to 50 mg, and lobaplatin ranged from 0 to 200 mg. After confirming the correct position of the catheter tip, the chemotherapeutic and embolic agents were infused under radiographic guidance. To control the correct administration of drugs and the occlusion of tumor vessels with flow stasis, a final angiography was performed. TACE combined with radiofrequency ablation (RFA) treatment were applied for HCC patients with a single nodule > 3 cm and ≤ 5 cm or those with 2-3 nodules ≤ 3 cm.

Outcome definition
As in previous reports[8,10,11], post-TACE liver failure in our study was modified and defined as the presence of any of the following conditions within one week after TACE: Increase in total bilirubin ≥ 17.1 μmol/L, increase in prothrombin time ≥ 3 s, new onset hepatic encephalopathy, and increase in ascites.

Data collection
All patients underwent blood examinations including routine blood tests, liver and kidney function tests, coagulation function tests, serum tumor markers, HBsAg, HBeAg, hepatitis B virus (HBV) DNA and anti-hepatitis C virus (HCV) antibody, prior to the procedure. HCV RNA was measured if a positive anti-HCV antibody was detected. Post-TACE liver function tests and coagulation function tests were conducted every 3 d within the first week after TACE. The serum samples were collected, transported and tested following the standard operating procedures of the Department of Medical Laboratory, Shanghai Public Health Clinical Center.

The assessment of post-TACE liver failure was performed at 7 d or earlier. Abdominal CT/MRI and chest CT were also performed prior to TACE procedures to assess the clinicopathological characteristics including main tumor size, tumor number, cirrhosis status, metastasis, portal vein tumor thrombus, vascular invasion, ascites and pleural effusion. Other medical information, including disease history and treatment history, was also collected. All TACE procedures were assessed separately.

Statistical analysis
Based on the variable types, Student’s t test and chi-square test were used to analyze the differences in variables between groups. The parameters related to the results were evaluated by univariate and multivariate logistic regression. The results are reported as odds ratios (OR) with 95% confidence intervals (CI). Parameters significantly associated with the outcomes in the multivariate logistic model were included in the risk prediction model by nomogram with the “rms” package in the R software program. A calibration plot was presented to evaluate the performance of the nomogram, which was also established in the “rms” package in the R program. The area under the receiver operating characteristic curve (AUROC) was computed to assess the prediction efficiency of the latent predictors. Stata
software version 16.0 (Stata Corp LLC, Texas, United States) was used. A two-sided \( P < 0.05 \) was considered significant.

**RESULTS**

**Baseline characteristics and laboratory parameters**

In total, 199 HCC patients who received TACE therapy were included in this study, and 70 patients (35.2%) developed post-TACE liver failure. As summarized in Table 1, more patients in the post-TACE liver failure group received microspheres plus gelatin embolization than in the nonpost-TACE liver failure group (24.3% vs 3.9%, \( P < 0.001 \), Table 1). The frequency of patients with a main tumor size ≥ 5 cm was significantly higher in the post-TACE liver failure group than in the nonpost-TACE liver failure group (58.6% vs 40.3%, \( P = 0.014 \), Table 1). More patients received combination therapy with RFA and had a resection surgery treatment history in the nonpost-TACE liver failure group than in the post-TACE liver failure group (\( P = 0.025 \) and \( P = 0.032 \), respectively, Table 1). Patients who developed post-TACE liver failure had significantly higher hematocrit, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBiL) and direct bilirubin (DBiL) levels than those without post-TACE liver failure (all \( P < 0.05 \), Table 1). However, patients who developed post-TACE liver failure had significantly lower serum cystatin C and creatinine levels and higher estimated glomerular filtration rate (eGFR) levels than those without post-TACE liver failure (all \( P < 0.05 \), Table 1). The other baseline clinical characteristics and laboratory parameters were not significantly distributed between these two groups (all \( P > 0.05 \), Table 1).

**Predictors for post-TACE liver failure**

Univariate logistic analysis revealed that microspheres plus gelatin embolization, RFA combination, main tumor size, resection history, diabetes, hematocrit, ALT, AST, gamma-glutamyl transferase, TBiL, DBiL, total bile acid, serum cystatin C, creatinine and eGFR levels were all potential predictors for post-TACE liver failure (all \( P < 0.1 \), Table 2). When these variables were included in the multivariate model, microspheres plus gelatin embolization and main tumor size > 5 cm were risk factors for the occurrence of post-TACE liver failure (OR: 4.4, 95%CI: 1.2-16.3, \( P = 0.027 \) and OR: 2.3, 95%CI: 1.05-5.3, \( P = 0.039 \), respectively, Table 2). Conversely, HCC patients who underwent tumor resection surgery before the TACE procedure had a lower risk for post-TACE liver failure (OR: 0.4, 95%CI: 0.2-0.95, \( P = 0.039 \), Table 2).

**Nomogram and ROC models of predictors**

Based on the multivariate logistic analysis, we included microspheres plus gelatin embolization, main tumor size and liver tumor resection history as predictors to establish a nomogram model, which is shown in Figure 1A. The calibration curve of the nomogram model with internal bootstrapping was calculated and is presented in Figure 1B.

ROC analysis was also performed to evaluate the predictive ability of the indicators. As shown in Figure 2, the AUROCs of microspheres plus gelatin embolization, main tumor size, liver tumor resection history, and the nomogram model were 0.602, 0.591, 0.569 and 0.61, respectively (Figure 2). Unfortunately, all the AUROCs were less than 0.7, leading to an unsatisfactory discrimination ability of these parameters for screening post-TACE liver failure in HCC patients.

**Frequency of post-TACE liver failure in subgroups**

HCC patients who received microspheres plus gelatin embolization developed post-TACE liver failure more frequently than those without microspheres combined with gelatin embolization (17/22, 77.3% vs 53/177, 29.9%, \( P < 0.001 \), Figure 3A). Patients with a main tumor size ≥ 5 cm experienced post-TACE liver failure significantly more frequently than those with a main tumor size < 5 cm (41/93, 44.1% vs 29/106, 27.4%; \( P = 0.014 \), Figure 3B). The incidence of post-TACE liver failure was significantly lower in HCC patients with a tumor resection history than in those without a liver tumor surgery history (11/49, 22.4% vs 39.3%, \( P = 0.032 \), Figure 3C).

**DISCUSSION**

The greatest concerns for TACE procedures are toxicity and safety issues. Post-TACE liver failure is one of the most severe complications and can lead to significant morbidity and mortality[15]. According to previous reports[8-11,13], post-TACE liver failure occurs frequently in HCC patients. In our study, post-TACE liver failure occurred in approximately 35% of HCC patients, regardless of whether they were TACE naïve patients or patients who received TACE treatment several times. To avoid the risk of post-TACE liver failure, early detection and prediction are of great importance in addressing TACE approaches.
Table 1 Baseline characteristics and laboratory parameters of hepatocellular carcinoma patients received post-transarterial chemoembolization

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n = 199)</th>
<th>None post-TACE liver failure (n = 129)</th>
<th>Post-TACE liver failure (n = 70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean ± SD</td>
<td>59.4 ± 10.9</td>
<td>59.7 ± 11.1</td>
<td>58.9 ± 10.7</td>
<td>0.59</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>157 (78.9)</td>
<td>105 (81.4)</td>
<td>52 (74.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Metastasis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal/adrenal</td>
<td>5 (2.5)</td>
<td>5 (3.9)</td>
<td>0 (0)</td>
<td>0.095</td>
</tr>
<tr>
<td>Abdomen/pelvis</td>
<td>6 (3.0)</td>
<td>4 (3.1)</td>
<td>2 (2.9)</td>
<td>0.92</td>
</tr>
<tr>
<td>Lymphnode</td>
<td>5 (2.5)</td>
<td>3 (2.3)</td>
<td>2 (2.9)</td>
<td>0.82</td>
</tr>
<tr>
<td>Bone</td>
<td>8 (4.0)</td>
<td>7 (5.4)</td>
<td>1 (1.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Lung</td>
<td>10 (5.0)</td>
<td>5 (3.9)</td>
<td>5 (7.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Intrahepatic</td>
<td>11 (5.5)</td>
<td>5 (3.9)</td>
<td>6 (8.6)</td>
<td>0.17</td>
</tr>
<tr>
<td>Pleural effusion, n (%)</td>
<td>21 (10.6)</td>
<td>15 (11.6)</td>
<td>6 (8.6)</td>
<td>0.50</td>
</tr>
<tr>
<td>Ascites, n (%)</td>
<td>59 (29.6)</td>
<td>38 (29.5)</td>
<td>21 (30.0)</td>
<td>0.94</td>
</tr>
<tr>
<td>FVTT, n (%)</td>
<td>56 (28.1)</td>
<td>33 (25.6)</td>
<td>23 (32.9)</td>
<td>0.28</td>
</tr>
<tr>
<td>Vascular invasion, n (%)</td>
<td>16 (8.0)</td>
<td>13 (10.1)</td>
<td>3 (4.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Tumor number, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>1</td>
<td>71 (37.8)</td>
<td>44 (36.1)</td>
<td>27 (40.9)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>27 (14.4)</td>
<td>18 (14.8)</td>
<td>9 (13.6)</td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>90 (47.9)</td>
<td>60 (49.2)</td>
<td>30 (45.5)</td>
<td></td>
</tr>
<tr>
<td>Times of TACE prior to inclusion, median (IQR)</td>
<td>1 (0, 3)</td>
<td>1 (0, 2)</td>
<td>1 (0, 3)</td>
<td>0.82</td>
</tr>
<tr>
<td>Embolization, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microspheres</td>
<td>55 (27.6)</td>
<td>33 (25.6)</td>
<td>22 (31.4)</td>
<td>0.378</td>
</tr>
<tr>
<td>Gelatin</td>
<td>20 (10.1)</td>
<td>12 (9.3)</td>
<td>8 (11.4)</td>
<td>0.634</td>
</tr>
<tr>
<td>Microspheres plus gelatin</td>
<td>22 (11.1)</td>
<td>5 (3.9)</td>
<td>17 (24.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lipiodol, mL, median (IQR)</td>
<td>10 (5, 10)</td>
<td>8 (5, 10)</td>
<td>10 (6, 10)</td>
<td>0.17</td>
</tr>
<tr>
<td>Pirarubicin, mg, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>0</td>
<td>55 (27.6)</td>
<td>37 (28.7)</td>
<td>18 (25.7)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>36 (18.1)</td>
<td>25 (19.4)</td>
<td>11 (15.7)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>99 (49.7)</td>
<td>63 (48.8)</td>
<td>36 (51.4)</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>4 (2.0)</td>
<td>2 (1.6)</td>
<td>2 (2.9)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>4 (2.0)</td>
<td>2 (1.6)</td>
<td>2 (2.9)</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Lobaplatin, mg, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>0</td>
<td>45 (22.6)</td>
<td>28 (21.7)</td>
<td>17 (24.3)</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>1 (0.5)</td>
<td>1 (0.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>152 (76.4)</td>
<td>100 (77.5)</td>
<td>52 (74.3)</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Combination with RFA, n (%)</td>
<td>22 (11.1)</td>
<td>19 (14.7)</td>
<td>3 (4.3)</td>
<td>0.025</td>
</tr>
<tr>
<td>Main tumor size ≥ 5cm, n (%)</td>
<td>93 (46.7)</td>
<td>52 (40.3)</td>
<td>41 (58.6)</td>
<td>0.014</td>
</tr>
<tr>
<td>CNLC, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.071</td>
</tr>
<tr>
<td>1</td>
<td>93 (46.7)</td>
<td>66 (51.2)</td>
<td>27 (38.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>III</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 (25.1)</td>
<td>26 (20.2)</td>
<td>24 (34.3)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>185 (93.0)</td>
<td>121 (93.8)</td>
<td>64 (91.4)</td>
<td></td>
</tr>
<tr>
<td>CTP score, median (IQR)</td>
<td>5 (5, 6)</td>
<td>5 (5, 6)</td>
<td>6 (5, 6)</td>
<td></td>
</tr>
<tr>
<td>MELD score, median (IQR)</td>
<td>29.6 (27.3, 32.2)</td>
<td>29.7 (27.4, 32.3)</td>
<td>29.5 (27.1, 32.0)</td>
<td></td>
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Treatment history, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib</th>
<th>Resection</th>
<th>Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21 (10.6)</td>
<td>38 (29.5)</td>
<td>27 (38.6)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>43 (21.6)</td>
<td>27 (20.9)</td>
<td>16 (22.9)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>29 (14.6)</td>
<td>23 (17.8)</td>
<td>6 (8.6)</td>
</tr>
</tbody>
</table>

Blood routine tests, median (IQR)

<table>
<thead>
<tr>
<th></th>
<th>WBC, 10^3/mm^3</th>
<th>RBC, 10^6/mm^3</th>
<th>Hemoglobin, g/L</th>
<th>Hematocrit, %</th>
<th>PLT, 10^9/mm^3</th>
<th>Neutrophils, 10^9/mm^3</th>
<th>Lymphocytes, 10^9/mm^3</th>
<th>Monocytes, 10^9/mm^3</th>
<th>Hypersensitive CRP, mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.7 (3.5, 6.0)</td>
<td>4.6 (3.4, 6.1)</td>
<td>4.1 (3.6, 4.5)</td>
<td>37.0 (6.3)</td>
<td>2.9 (2.0, 3.9)</td>
<td>1.1 (0.8, 1.4)</td>
<td>0.4 (0.3, 0.6)</td>
<td>3.0 (0.7, 23.5)</td>
<td>3.6 (0.7, 23.5)</td>
</tr>
</tbody>
</table>

Liver functions, median (IQR)

<table>
<thead>
<tr>
<th></th>
<th>ALT, U/L</th>
<th>AST, U/L</th>
<th>GGT, U/L</th>
<th>AKP, U/L</th>
<th>TBL, μmol/L</th>
<th>DBIL, μmol/L</th>
<th>TBA, μmol/L</th>
<th>Albumin, g/L</th>
<th>Cholinesterase, U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29 (20, 44)</td>
<td>38 (26, 61)</td>
<td>78 (41, 175)</td>
<td>137 (97, 197)</td>
<td>19 (13.1, 28.7)</td>
<td>8.5 (5.9, 12.7)</td>
<td>17.7 (8.2, 40.5)</td>
<td>37.8 (33.7, 42.1)</td>
<td>5224 (3698, 6826)</td>
</tr>
</tbody>
</table>

Kidney functions, median (IQR)

<table>
<thead>
<tr>
<th></th>
<th>Serum cystatin C, mg/L</th>
<th>Urea, mmol/L</th>
<th>Creatinine, μmol/L</th>
<th>eGFR, mL/(min.1.73 m^2)</th>
<th>Serum ammonia, median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.97 (0.8, 1.13)</td>
<td>4.8 (4.0, 5.9)</td>
<td>62.4 (52.7, 74.5)</td>
<td>116.1 (93.6, 137.9)</td>
<td>45 (34, 60)</td>
</tr>
</tbody>
</table>

Coagulation function tests, median (IQR)

<table>
<thead>
<tr>
<th></th>
<th>PTA, %</th>
<th>Prothrombin time, s</th>
<th>INR</th>
<th>APTT, s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>84 (73.5, 93)</td>
<td>14.4 (13.8, 15.5)</td>
<td>1.11 (1.04, 1.22)</td>
<td>39.3 (36.4, 42.1)</td>
</tr>
</tbody>
</table>

|                      | 83 (73, 92) | 14.5 (13.8, 15.5)   | 1.12 (1.05, 1.22) | 38.9 (36.7, 42)    |
|                      | 86 (74, 95) | 14.3 (13.5, 15.4)   | 1.1 (1.03, 1.21)  | 39.4 (36.3, 42.9)  |

<p>|                      |        | 0.3 (0, 0.6)        | 0.53       | 1.00       |
|                      |        | 0.001               | 0.007      | 0.27       |</p>
<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
</tr>
<tr>
<td>Microsphere plus gelatin embolization, yes vs no</td>
<td>8.0</td>
<td>2.8-22.7</td>
</tr>
<tr>
<td>Combination with RFA, yes vs no</td>
<td>0.3</td>
<td>0.1-0.9</td>
</tr>
<tr>
<td>Main tumor size ≥ 5 cm, yes vs no</td>
<td>2.1</td>
<td>1.2-3.8</td>
</tr>
<tr>
<td>Resection history, yes vs no</td>
<td>0.4</td>
<td>0.2-0.9</td>
</tr>
<tr>
<td>Diabetes, yes vs no</td>
<td>0.4</td>
<td>0.2-1.1</td>
</tr>
<tr>
<td>Hematocrit, per increase 1%</td>
<td>1.1</td>
<td>1.0-1.1</td>
</tr>
<tr>
<td>ALT, per increase 1 U/L</td>
<td>1.01</td>
<td>1.0-1.03</td>
</tr>
<tr>
<td>AST, per increase 1 U/L</td>
<td>0.99</td>
<td>0.98-1.004</td>
</tr>
<tr>
<td>GGT, per increase 1 U/L</td>
<td>1.0</td>
<td>1.0-1.0</td>
</tr>
<tr>
<td>TBiL, μmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>1-2 ULN</td>
<td>1.8</td>
<td>1.0-3.5</td>
</tr>
<tr>
<td>≥ 2 ULN</td>
<td>2.3</td>
<td>1.0-5.3</td>
</tr>
<tr>
<td>DBiL, per increase 1 μmol/L</td>
<td>1.8</td>
<td>1.0-3.2</td>
</tr>
<tr>
<td>TBA ≥ 17.7μmol/L, yes vs no</td>
<td>1.8</td>
<td>1.0-3.3</td>
</tr>
<tr>
<td>Serum cystatin C, per increase 1 mg/L</td>
<td>0.4</td>
<td>0.1-1.0</td>
</tr>
<tr>
<td>Creatinine, per increase 1 μmol/L</td>
<td>0.98</td>
<td>0.97-1.0</td>
</tr>
<tr>
<td>eGFR, per increase 1 ml/(min·1.73 m²)</td>
<td>1.01</td>
<td>1.0-1.02</td>
</tr>
</tbody>
</table>

Only variables significantly associated with post-transarterial chemoembolization liver failure in univariate analysis (P < 0.10) were presented.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; direct bilirubin; eGFR: Estimated glomerular filtration rate; GGT: Gamma-glutamyl transferase; RFA: Radiofrequency ablation; TBA: Total bile acid; TBiL: Total bilirubin; U/LN: Upper limit of normal; OR: Odds ratio; CI: Confidence interval.

This study indicated that microspheres plus gelatin embolization beyond chemotherapy drugs might contribute to a higher risk of post-TACE liver failure. Microsphere embolization is recommended because their controllable size distribution and spherical shape may improve and strengthen the embolization effect. The microsphere embolization strategy for vascular catheter calibration can maximize tumor necrosis. Gelatin embolization also demonstrated beneficial clinical outcomes in the
Figure 1 Nomogram for probability of post-transarterial chemoembolization liver failure in hepatocellular carcinoma patients. A: The nomogram model; B: The calibration curve of the nomogram model with internal validation through bootstrapping. TACE: Transarterial chemoembolization.

Figure 2 Receiver operating characteristic curves of predictors for post-transarterial chemoembolization liver failure. A: Receiver operating characteristic (ROC) of microspheres plus gelatin embolization; B: ROC of main tumor size > 5 cm; C: ROC of resection history; D: ROC of the nomogram model. AUC: Area under the curve; CI: Confidence interval.

treatment of HCC[18]. However, TACE includes hepatic artery infusion che-motherapy and embolization. Therefore, arterial infusion of chemotherapy drugs and embolization agents could be the main causes of liver failure after TACE[19]. The fragmentation of microspheres under pressure may cause nontargeted embolization and cause tissue necrosis[20]. The combination of microspheres and gelatin could induce more arterial trauma than the single use of microspheres or gelation sponge particles. The reduction in arterial blood supply by arterial trauma may induce liver injury and inhibit the recovery of liver dysfunction after embolization[21]. Thus, the properties of the microspheres should be fully evaluated, including size distribution, compressibility, suspension evaluation, catheter transferability, and failure stress. In addition, gelatin-based embolization may lead to early recovery of blood flow or can lead to permanent occlusion due to its unpredictable enzymatic degradation profile[22]. Cautious investigation of the risks and benefits of gelatin-based embolization is suggested for TACE procedures.

In line with a previous report, TACE in patients with tumors larger than 5 cm predicts postprocedure liver failure[23]. Tumor size is a vital parameter that should be considered in the selection of multidisciplinary treatment strategies[24]. Multiple studies have demonstrated that a larger tumor size correlates with worse survival in HCC patients who receive TACE treatment[25-27]. There is consensus that a larger tumor size increases treatment difficulties, aggravates complications and deteriorates outcomes in HCC patients. Current evidence indicates that TACE plus sorafenib significantly improves
progression-free survival over TACE alone in patients with unresectable HCC\cite{28}. According to these findings, it is essential to avoid combined embolization with microspheres and gelatin during the TACE procedure in unresected HCC patients with tumors larger than 5 cm in size. Unfortunately, no alternative solution has been envisaged to treat these large lesions in the current report.

The current guidelines recommend that surgical therapies, including resection and transplantation are the first-line choice for early-stage HCC patients\cite{14,29}. This study revealed that patients who received liver tumor resection had a lower risk for post-TACE liver failure when they received TACE therapy in the late stages. Undoubtedly, the hepatic functional reserve of patients who received liver tumor resection was relatively better than that of HCC patients who had not undergone tumor resection. Inadequate hepatic functional reserve is one of the determining factors for post-hepatectomy liver failure\cite{30,31}. Hepatic functional reserve has been proven to be associated with treatment selection, tumor recurrence and survival in patients with advanced HCC\cite{32,33}. In clinical practice, preoperative assessment of hepatic functional reserve is of great importance for prevention of post-TACE liver failure, regardless of liver tumor resection history. Previous reports indicate that poor hepatic functional reserve, high-dose chemotherapy drug infusion, portal vein thrombosis, ascites, gastrointestinal bleeding, elevated AFP, and history of multiple embolization operations are risk factors for predicting post-TACE liver failure\cite{8,10,11,13,15,21,34}. In addition, several models, including the CTP score, Barcelona Clinic Liver Cancer staging, Mode for End-stage Liver Disease score, and the Hepatoma Arterial-embolisation Prognostic score, were helpful for avoiding the post chemoembolization toxicity and treatment decision-making\cite{3,35-37}. Considering the various definitions of post-TACE liver failure in these studies and our analysis, future research is still urgently needed to investigate candidates that could predict the occurrence of post-TACE liver failure.

This study has some limitations. The primary limitation is that this study had a relatively short follow up period, leading to no observations of recovery or irreversible post-TACE liver failure. Second, the retrospective design with a relatively small sample size in a single center might reduce its representativeness, and there was no calculation or justification of the sample size selected in this study. Third, the assessment of ascites increases in the definition of post-TACE liver failure brought subjectivity, and potential biases such as information bias and selection bias existed in this retrospective study. Fourth, the predictive performance of the risk factors and nomogram model for post-TACE liver failure is not promising enough for clinical application. However, our results indicate that post-TACE liver failure commonly occurred, especially in HCC patients who received microspheres plus gelatin embolization therapy, and those with larger main tumor sizes. A good hepatic functional reserve should be favorable for the occurrence of post-TACE liver failure.

**CONCLUSION**

Post-TACE liver failure occurs frequently in HCC patients. However, there is no uniform definition of post-TACE liver failure. The incidence of post-TACE liver failure varies from 0 to 60% globally. This retrospective study concluded that microspheres plus gelation embolization and large tumor size might...
be involved in the increased risk of post-TACE liver failure. Cautious preprocedure investigation of the risks and benefits of TACE therapy in HCC patients with large tumors is suggested. Embolization approaches should also be evaluated to avoid the risk of post-TACE liver failure. In addition, HCC patients who had undergone liver tumor resection had a lower risk for post-TACE liver failure when they received TACE therapy in the late stages. Moreover, early detection and prediction of post-TACE liver failure by monitoring the hepatic functional reserve should be addressed. Conclusively, it is essential to avoid combined embolization with microspheres and gelatin during the TACE procedure in unresected HCC patients with large tumor sizes.

**ARTICLE HIGHLIGHTS**

**Research background**
Post-transarterial chemoembolization (TACE) liver failure occurs frequently in hepatocellular carcinoma (HCC) patients received TACE procedure.

**Research motivation**
Identification of risk factors for post-TACE liver failure is important for TACE treatment decision-making.

**Research objectives**
The aim of this retrospective study was to assess the occurrence rate and predictive factors of post-TACE liver failure in HCC patients.

**Research methods**
Baseline characteristics and laboratory parameters of HCC patients received TACE therapy were assessed.

**Research results**
A total of 35.2% (70/199) HCC patients occurred post-TACE liver failure after TACE therapy. Logistic models indicated that microspheres plus gelatin embolization and main tumor size > 5 cm were risk predictors for the occurrence of post-TACE liver failure. Conversely, HCC patients who underwent tumor resection surgery before the TACE procedure had a lower risk for post-TACE liver failure.

**Research conclusions**
Microspheres plus gelatin embolization and main tumor size might be risk factors for the occurrence of post-TACE liver failure in HCC patients, while tumor resection history could be a favorable factor for post-TACE liver failure.

**Research perspectives**
Pre-TACE assessment including embolization strategy, tumor size, and hepatic functional reserve is of great importance for avoiding post-TACE liver failure. More studies need to be done to confirm these findings.

**FOOTNOTES**

**Author contributions:** Yang ZG and Tang BZ conceived and designed the study; Yuan M wrote the manuscript; Chen TY, Chen XR, Lu YF, Shi J, Zhang WS, Tang BZ, and Ye C analyzed and interpreted the data; Yang ZG and Tang BZ were responsible for revising the manuscript for important intellectual content; and all authors read and approved the final version.

**Supported by** Shanghai Science and Technology Committee, No. 19401931600; Shanghai Municipal Health Commission, No. 2020LZ001; and Health Commission of Pudong New District, Shanghai, No. PDZY-2021-0706.

**Institutional review board statement:** The study was reviewed and approved by the Ethics Committee, Shanghai Public Health Clinical Center, Fudan University (approval No.2021-S062-01).

**Conflict-of-interest statement:** All the authors declare that there are no conflicts of interest related to this study.

**Data sharing statement:** No additional data are available.

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REFERENCES


Yuan M et al. Risk factors of post-TACE liver failure


Clinical significance of half-hepatic blood flow occlusion technology in patients with hepatocellular carcinoma with cirrhosis

Dong Liu, Jian-Ming Fang, Xian-Qi Chen

Abstract

BACKGROUND
Most patients with primary hepatocellular carcinoma (HCC) have a history of chronic hepatitis B and usually present with varying degrees of cirrhosis. Owing to the special nature of liver anatomy, the blood vessel wall in the liver parenchyma is thin and prone to bleeding. Heavy bleeding and blood transfusion during hepatectomy are independent risk factors for liver cancer recurrence and death. Various clinical methods have been used to reduce intraoperative bleeding, and the Pringle method is most widely used to prevent blood flow to the liver.

AIM
To investigate the effect of half-hepatic blood flow occlusion after patients with HCC and cirrhosis undergo hepatectomy.

METHODS
This retrospective study included 88 patients with HCC and liver cirrhosis who underwent hepatectomy in our hospital from January 2017 to September 2020. Patients were divided into two groups based on the following treatment methods: the research group (n = 44), treated with half-hepatic blood flow occlusion technology and the control group (n = 44), treated with total hepatic occlusion. Differences in operation procedure, blood transfusion, liver function, tumor markers, serum inflammatory response, and incidence of surgical complications were compared between the groups.

RESULTS
The operation lasted longer in the research group than in the control group (273.0 ± 24.8 min vs 256.3 ± 28.5 min, P < 0.05), and the postoperative anal exhaust time was shorter in the research group than in the control group (50.0 ± 9.7 min vs 55.1 min).
± 10.4 min, \( P < 0.05 \)). There was no statistically significant difference in incision length, surgical bleeding, portal block time, drainage tube indwelling time, and hospital stay between the research and control groups \(( P > 0.05 \)). Before surgery, there were no significant differences in serum alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin, and prealbumin levels between the research and control groups \(( P > 0.05 \)). Conversely, 24 and 72 h after the operation the respective serum ALT \((378.61 ± 77.49 \text{ U/L} \text{ and } 246.13 ± 54.06 \text{ U/L})\) and AST \((355.30 ± 69.50 \text{ U/L} \text{ and } 223.47 ± 48.64 \text{ U/L})\) levels in the research group were significantly lower \(( P < 0.05 \) than those in the control group \((ALT, 430.58 ± 83.67 \text{ U/L} \text{ and } 281.35 ± 59.61 \text{ U/L}; \text{AST, } 416.49 ± 73.03 \text{ U/L} \text{ and } 248.62 ± 50.10 \text{ U/L})\). The operation complication rate did not significantly differ between the research group (15.91\%) and the control group (22.73\%; \( P > 0.05 \)).

**CONCLUSION**

Half-hepatic blood flow occlusion technology is more beneficial than total hepatic occlusion in reducing liver function injury in hepatectomy for patients with HCC and cirrhosis.

**Key Words:** Hepatocirrhosis; Hepatocellular carcinoma; Hepatectomy; Hepatic occlusion; Liver function

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**Core Tip:** There are differences in the selection of different blood-flow blocking techniques during hepatocellular carcinoma (HCC) surgery. We explore surgical effect of half hepatic blood flow occlusion and liver function recovery of patients with hepatocirrhosis HCC in hepatectomy.

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**INTRODUCTION**

Hepatocellular carcinoma (HCC) accounts for 90% of all primary liver tumors\(^1\). Most patients with HCC often also have cirrhosis, and the recurrence of microvascular tumor thrombi has been increasing. Currently, radical surgery is the preferred treatment for HCC; however, massive intraoperative bleeding and blood transfusion may increase the incidence of postoperative complications, mortality, and the possibility of recurrence and metastasis of HCC\(^2,3\). The vascular distribution of the liver is more complex, and the blood supply is rich. Therefore, effective control of bleeding during hepatectomy has been the focus of liver surgery research\(^4\). In 1988, researchers proposed a method of vascular occlusion during hepatectomy that could be used to control intraoperative blood loss. The classical Pringle total hepatic occlusion and selective semi-hepatic occlusion techniques are mainly used in clinical practice\(^5\). However, there are differences in the selection of different blood-flow blocking techniques during tumor surgery. This study selected patients with HCC and liver cirrhosis scheduled to undergo hepatectomy in our hospital to explore the postoperative surgical effect of half hepatic blood flow occlusion and liver function recovery in this patient population.

**MATERIALS AND METHODS**

**General data**

This retrospective single-blinded study included 88 patients with HCC and liver cirrhosis who underwent hepatectomy from January 2017 to September 2020 in our hospital and were divided into an observation group and a control group (44 patients in each group). The inclusion criteria were based on the diagnostic criteria for patients with HCC in the code for the diagnosis and treatment of primary liver cancer (2011 edition)\(^6\) as follows: confirmed preoperative computed tomography and magnetic resonance imaging examinations or confirmed liver biopsy, age of ≤ 75 years, mild cirrhosis, preoperative Child–Pugh liver function grade A or B\(^7\), and tumor diameter of 2.0–6.0 cm. This study met the relevant requirements of the Medical Ethics Committee, and written informed consent was obtained from the patients. The exclusion criteria were as follows: patients with metastasis to other abdominal organs, with other malignant tumors, history of cerebrovascular or myocardial infarction within the last 6 mo, with history of parasitic diseases such as liver echinococcosis, and with anemia or...
malnutrition.

The research group included patients aged 50–75 years, with an average age of 60.6 ± 5.0 years (26 men and 18 women). Forty patients had preoperative Child-Pugh grade A and four patients had grade B. The mean lesion diameter was 5.18 ± 1.00 cm. History of hepatitis B virus infection was noted in 32 cases. The mean serum alpha-fetoprotein (AFP) value was 240.8 ± 75.6 ng/L. Regarding the surgical resection scope, there were ≥3 Liver segments in 18 cases and < 3 liver segments in 26 cases. The control group included patients aged 48–75 years, with an average age of 61.3 ± 5.5 years (22 men and 22 women). Thirty-seven patients had preoperative Child-Pugh grade A and seven patients had grade B. The mean lesion diameter was 5.08 ± 1.30 cm. History of hepatitis B virus infection was noted in 27 cases, and the mean serum AFP value was 228.6 ± 66.3 ng/L. Regarding the surgical resection scope, there were ≥3 Liver segments in 14 cases and < 3 liver segments in 30 cases. There was no statistically significant difference in the baseline data between the groups ($P > 0.05$), as shown in Table 1.

**Operation methods**

All patients underwent a right upper abdominal incision under general anesthesia. The site of the lesion and scope of resection were determined after entering the abdomen. All liver tissues were removed using forceps, and the duct with a larger wound surface was sutured and tied.

The control group was treated with the Pringle total hepatic blood flow occlusion technique, in which partial heptectomy was performed after the hepatoduodenal ligament and entire hepatic blood flow were blocked with a normal drainage tube through the Venturi hole tightly the hepatoduodenal ligament to completely block the hepatic artery and portal vein. Every operation was controlled for 15 min, depending on the ease of operation and adjustment of the block number of operating time. If the liver tumor could not be removed within the period of closure, the operation had to be repeated for 5–10 min intermittently until the liver tumor was removed and blocked at most twice.

Half-hepatic blood flow occlusion technology was used in the research group. The first hepatic portal was dissected, and the left and right hepatic veins, left and right portal veins, and left and right hepatic ducts were bluntly separated to block the branches of the hepatic artery and portal vein on the affected side to form a local ischemic area. Hepatectomy was performed along the edge of this ischemic area. Vascular forceps were used to externally separate the hilum at the upper margin of the lateral sulcus of the affected side against the Glisson sheath. The fingers of the left hand were guided behind the hepatic portal, and the vascular forceps were threaded out from behind the Glisson sheath and blocked the affected side of the liver into the hepatic blood flow with the blocking band, for < 15 min each time, and blocked again 5 min after opening. After liver resection, the wound was treated, the blood flow pathway was opened, and an abdominal drainage tube was placed.

**Observation indicators and detection methods**

Operation time, incision length, surgical bleeding, portal block time, postoperative anal exhaust time, drainage tube indwelling time, and hospital stay were compared between the groups. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), prealbumin (PA), AFP, carcinoembryonic antigen (CEA), α-L fucosylase (AFU), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) levels before and after surgery, C-reactive protein (CRP) levels, and postoperative complications were also compared between the groups.

After surgery, 5 mL fasting venous blood was collected from the patient and centrifuged at 3000 rpm for 5 min; the supernatant was collected to detect serum ALT, AST, TBIL, and PA levels. TBIL levels were determined using the vanadate method. The kit was provided by Beijing Jiuqiang Biotechnology Co., Ltd. The normal reference range was 3.0–20.0 μmol/L. AST and ALT were continuously monitored by Ningbo Purui Biotechnology Co., Ltd., with the normal reference range being 0–40 U/L. The PA immunotransmission turbidimetry kit was provided by Shanghai Shenfeng Biological Reagent Co., Ltd., with a normal reference range of 200–400 mg/L. The levels of AFP, AFU, and CEA in the serum were detected using a C6000 automatic immunochemiluminescence analyzer provided by Roche. All operations were carried out in strict accordance with the requirements determined by Wuhan Youersheng Bioengineering Co., LTD. The normal reference values of the tumor markers were: AFP < 15 ng/mL, AFU < 40 U/L, CEA < 5.0 ng/mL, and CA19-9 < 27 U/L.

**Statistical analysis**

SPSS 21.0 was used for data analysis. ALT, AST, TBIL, and other measurement data of the two groups are expressed as mean ± SD, and the $t$-test was used for inter-group comparisons. For enumeration data, the $\chi^2$-test was used for inter-group comparisons. Statistical significance was set at $P < 0.05$.

**RESULTS**

**Comparison of surgical process indicators between the two groups**

The operation group in the research group was longer than that of the control group ($P < 0.05$).
Table 1 Comparison of baseline data between the two groups of patients, n (%)

<table>
<thead>
<tr>
<th>Normal information</th>
<th>Research group (n = 44)</th>
<th>Control group (n = 44)</th>
<th>t/χ² value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>60.6 ± 5.0</td>
<td>61.3 ± 5.5</td>
<td>-0.625</td>
<td>0.534</td>
</tr>
<tr>
<td>Lesion diameter (cm)</td>
<td>5.18 ± 1.00</td>
<td>5.08 ± 1.30</td>
<td>0.404</td>
<td>0.687</td>
</tr>
<tr>
<td>Serum AFP (ng/L)</td>
<td>240.8 ± 75.6</td>
<td>228.6 ± 66.3</td>
<td>0.805</td>
<td>0.423</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.733</td>
<td>0.392</td>
</tr>
<tr>
<td>Male</td>
<td>26 (59.09)</td>
<td>22 (50.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (40.91)</td>
<td>22 (50.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh stage</td>
<td></td>
<td></td>
<td>1.252</td>
<td>0.263</td>
</tr>
<tr>
<td>A stage</td>
<td>40 (100)</td>
<td>37 (84.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B stage</td>
<td>4 (9.09)</td>
<td>7 (15.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus infection</td>
<td></td>
<td></td>
<td>1.286</td>
<td>0.257</td>
</tr>
<tr>
<td>Yes</td>
<td>32 (72.73)</td>
<td>27 (61.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12 (27.27)</td>
<td>17 (38.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical resection range</td>
<td></td>
<td></td>
<td>0.786</td>
<td>0.375</td>
</tr>
<tr>
<td>≥ 3 liver segments</td>
<td>18 (40.91)</td>
<td>14 (31.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 liver segments</td>
<td>26 (59.09)</td>
<td>30 (68.18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Postoperative anal exhaust time in the research group was shorter than that in the control group (P < 0.05), with no statistically significant difference in incision length, surgical bleeding, portal block time, drainage tube indwelling time, and hospital stay between the operation group and the control group (P > 0.05, Table 2).

Comparison of liver function indexes between two groups of patients
Before surgery, there were no significant differences in serum ALT, AST, TBIL, and PA levels between the research and control groups (P > 0.05). Meanwhile, 24 h and 72 h after operation, the serum ALT and AST values in the research group were lower than those in the control group (P < 0.05, Table 3).

Comparison of tumor marker levels between the two groups
Before surgery, there were no significant differences in serum AFP, CEA, and AFU levels between the research group and the control group (P > 0.05). One month after surgery, the serum AFP, CEA, and AFU levels in the two groups were lower than those before surgery (P < 0.05), and there was no statistically significant difference between the two groups (P > 0.05, Table 4).

Comparison of inflammatory factors between the two groups of patients before and after surgery
Before surgery, there were no significant differences in serum TNF-α, IL-6, and CRP levels between the research and control groups (P > 0.05). The levels of TNF-α and IL-6 in the research group were lower than those in the control group (P < 0.05, Table 5).

Comparison of operation complication rate between the two groups
The operation complication rate of the research group was 15.91%, whereas that of the control group was 22.73%, and the difference was not statistically significant (P > 0.05, Figure 1).

DISCUSSION
Total hepatic blood flow occlusion during surgical resection can completely block blood return to the portal vein system, resulting in gastrointestinal tract hyperemia, impaired mucosal barrier function, and high susceptibility to bacterial and toxin infections. Long-term blocking of portal blood flow can lead to portal vein and superior mesenteric vein thromboses[8-10]. More importantly, the blood entering the liver causes ischemic reperfusion injury of the liver parenchyma and distal organs after the blood flow is restored, and the liver function is seriously impaired. Theoretically, local hemo-occlusion in the affected segment of the patient’s liver is better, with minimal damage to liver function and in line with the concepts of anatomic hepatectomy and precise hepatectomy[11-13]. However, the operation process is complicated and requires mastery of color ultrasound-guided puncture technology, which has not been
In our study, the operation lasted longer in the research group than in the control group. There was no statistically significant difference in incision length, surgical bleeding, portal block time, drainage tube indwelling time, and hospital stay between the operation and control groups, indicating that control of half-hepatic blood flow during the operation was similar to that during use of the complete hepatic occlusion technique, which could effectively reduce bleeding. The half-hepatic blood flow occlusion technique requires detailed intrathecal dissection of the first hilum of the liver, thus increasing the difficulty of the operation and operative time. The technique of hepatic blood flow occlusion for hepatectomy can easily lead to liver ischemia and hypoxia, which can cause liver tissue damage and liver function impairment[18].

Meanwhile, 24 and 72 h after the operation, the serum ALT and AST levels in the research group were significantly lower than those in the control group, indicating that the half-hepatic blood flow occlusion technique is superior for postoperative liver function recovery. The reason is that half-hepatic occlusion does not markedly influence the hemodynamics, and

**,P < 0.05 vs this group before surgery.
ALT: Alanine transaminase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; PA: Prealbumin.
Table 4 Comparison of tumor marker levels between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Index</th>
<th>Research group (n = 44)</th>
<th>Control group (n = 44)</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFU (U/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>66.41 ± 9.51</td>
<td>68.18 ± 10.84</td>
<td>-0.814</td>
<td>0.418</td>
</tr>
<tr>
<td>1 mo after operation</td>
<td>27.04 ± 6.44*</td>
<td>29.95 ± 8.27</td>
<td>-1.842</td>
<td>0.069</td>
</tr>
<tr>
<td>AFP (ng/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>240.8 ± 75.6</td>
<td>228.6 ± 66.3</td>
<td>0.805</td>
<td>0.423</td>
</tr>
<tr>
<td>1 mo after operation</td>
<td>78.55 ± 18.04*</td>
<td>82.01 ± 20.63</td>
<td>-0.837</td>
<td>0.405</td>
</tr>
<tr>
<td>CEA (μg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>18.58 ± 4.20</td>
<td>20.03 ± 4.81</td>
<td>-1.506</td>
<td>0.136</td>
</tr>
<tr>
<td>1 mo after operation</td>
<td>3.77 ± 0.89*</td>
<td>4.01 ± 0.81</td>
<td>-1.323</td>
<td>0.189</td>
</tr>
</tbody>
</table>

*P < 0.05 vs this group before surgery.
AFU: Alpha-L f asosylase; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen.

Table 5 Comparison of inflammatory factors between the two groups of patients before and after surgery (mean ± SD)

<table>
<thead>
<tr>
<th>Index</th>
<th>Research group (n = 44)</th>
<th>Control group (n = 44)</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>54.23 ± 9.50</td>
<td>56.39 ± 9.11</td>
<td>-1.089</td>
<td>0.279</td>
</tr>
<tr>
<td>24 h after operation</td>
<td>97.41 ± 17.59</td>
<td>108.26 ± 18.25</td>
<td>-2.839</td>
<td>0.006</td>
</tr>
<tr>
<td>72 h after operation</td>
<td>70.55 ± 13.02</td>
<td>74.18 ± 14.40</td>
<td>-1.240</td>
<td>0.218</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>68.33 ± 13.20</td>
<td>70.53 ± 12.65</td>
<td>-0.798</td>
<td>0.427</td>
</tr>
<tr>
<td>24 h after operation</td>
<td>148.12 ± 21.04</td>
<td>167.00 ± 24.28</td>
<td>-3.898</td>
<td>0.000</td>
</tr>
<tr>
<td>72 h after operation</td>
<td>98.40 ± 13.27</td>
<td>102.73 ± 15.19</td>
<td>-1.424</td>
<td>0.158</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>4.91 ± 1.53</td>
<td>5.34 ± 1.58</td>
<td>-1.297</td>
<td>0.198</td>
</tr>
<tr>
<td>24 h after operation</td>
<td>18.48 ± 3.75</td>
<td>20.14 ± 4.43</td>
<td>-1.897</td>
<td>0.061</td>
</tr>
<tr>
<td>72 h after operation</td>
<td>14.20 ± 3.36</td>
<td>15.38 ± 4.28</td>
<td>-1.438</td>
<td>0.154</td>
</tr>
</tbody>
</table>

IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein.

Liu D et al. Half-hepatic blood flow occlusion technology in patients with HCC.

the mesenteric blood still flows back to the systemic circulation, avoiding gastrointestinal hyperemia, intestinal bacterium and endotoxin translocation, intestinal ventricular membrane injury, and liver regeneration. After operation, healthy hepatic arteries and portal veins remain open, not affecting the blood supply, thus avoiding ischemia-reperfusion injury and having less impact on liver function, especially in patients with hepatocirrhosis and other liver-related diseases. The rate of surgical complications in the research group was lower than that in the control group. This may be because the single block time of the half-hepatic blood flow occlusion technique is long, and the portal vein and hepatic artery branches at the lesion site are directly ligated or even separated; therefore, there is sufficient time for liver parenchyma dissection, hemostasis of the liver section, and bile leakage of the section to reduce the occurrence of surgical complications. In the past, the clinical diagnosis of patients with liver cancer was mainly based on AFP levels. Although the operation was simple, the detection sensitivity was not high, and it was easy to miss the diagnosis. In this study, 1 mo after surgery, the levels of serum AFP, CEA, and AFU in both groups were lower than those before surgery (P < 0.05), and there was no statistically significant difference between the groups. The reason for the analysis was that the patients were relieved of tumor cell growth and other factors after surgery, and the expression levels of AFP, AFU, and CEA decreased significantly.
Hepatectomy has always been the primary choice for patients with HCC and liver cirrhosis. Intraoperative blood flow occlusion with a half approach to the liver and a complete approach to the liver are both safe and effective, and the choice between the two methods is controversial\cite{19,20}. Therefore, the two methods were compared in this study. Changes in the operation process indicators were compared after the patients with hepatocirrhosis received different treatments. Postoperative liver function recovery and the occurrence of adverse reactions had certain reference values. Although half-hepatic blood flow occlusion is complicated and can prolong the operation time, it causes limited damage to liver function during the operation and is beneficial for the recovery of liver function after surgery, rendering it worthy of widespread clinical application. However, the sample size of this study was relatively small, and it is necessary to increase the sample size and detection indicators in future studies to verify the reliability of the results of this study.

**CONCLUSION**

In conclusion, half-hepatic blood flow occlusion technology is more beneficial than total hepatic occlusion in reducing liver function injury in patients with HCC and cirrhosis undergoing hepatectomy.

**ARTICLE HIGHLIGHTS**

**Research background**
Hepatocellular carcinoma (HCC) accounts for 90% of all primary liver tumors.

**Research motivation**
Currently, radical surgery is the preferred treatment for HCC.

**Research objectives**
This study aimed to investigate the effect of half-hepatic blood flow occlusion after patients with HCC and cirrhosis undergo hepatectomy.

**Research methods**
This retrospective single-blinded study included 88 patients with HCC and liver cirrhosis who underwent hepatectomy from January 2017 to September 2020 in our hospital and were divided into an observation group and a control group.

**Research results**
About 24 h and 72 h after the operation the respective serum alanine transaminase and aspartate aminotransferase levels in the research group were significantly lower than those in the control group.

**Research conclusions**
Half-hepatic blood flow occlusion technology is more beneficial than total hepatic occlusion in reducing liver function injury in patients with HCC and cirrhosis undergoing hepatectomy.
Research perspectives
However, the sample size of this study was relatively small, and it is necessary to increase the sample size and detection indicators in future studies.

FOOTNOTES

Author contributions: Liu D and Chen XQ designed the research study; Liu D performed the research; Fang JM contributed new reagents and analytic tools; Liu D analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

Supported by Key Scientific Research Project of Jinhua Science and Technology Bureau in 2020 Fund, No. 2020-3-069.

Institutional review board statement: The study was reviewed and approved by the Yongkang First People’s Hospital of Zhejiang Province Institutional Review Board.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: Dr. Chen XQ reports grants from Scientific Research Project of Jinhua Science and Technology Bureau in 2020, during the conduct of the study. No other conflict of interest to declare.

Data sharing statement: No additional data are available.

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REFERENCES


Retrospective Study

Which octogenarian patients are at higher risk after cholecystectomy for symptomatic gallstone disease? A single center cohort study

Fabrizio D’Acapito, Leonardo Solaini, Daniela Di Pietrantonio, Francesca Tauceri, Maria Teresa Mirarchi, Elena Antelmi, Francesca Flamini, Alessio Amato, Massimo Framarini, Giorgio Ercolani

Abstract

BACKGROUND
Incidence of gallstones in those aged ≥ 80 years is as high as 38%-53%. The decision-making process to select those oldest old patients who could benefit from cholecystectomy is challenging.

AIM
To assess the risk of morbidity of the “oldest-old” patients treated with cholecystectomy in order to provide useful data that could help surgeons in the decision-making process leading to surgery in this population.

METHODS
A retrospective study was conducted between 2010 and 2019. Perioperative variables were collected and compared between patients who had postoperative complications. A model was created and tested to predict severe postoperative morbidity.

RESULTS
The 269 patients were included in the study (193 complicated). The 9.7% of complications were grade 3 or 4 according to the Clavien-Dindo classification. Bilirubin levels were lower in patients who did not have any postoperative complications. American Society of Anesthesiologists scale 4 patients, performing a cholecdocholithotomy and bilirubin levels were associated with Clavien-Dindo > 2 complications ($P < 0.001$). The decision curve analysis showed that the proposed model had a higher net benefit than the treating all/none options between
threshold probabilities of 11% and 32% of developing a severe complication.

**CONCLUSION**
Patients with American Society of Anesthesiologists scale 4, higher level of bilirubin and need of choledocholithotomy are at the highest risk of a severely complicated postoperative course. Alternative endoscopic or percutaneous treatments should be considered in this subgroup of octogenarians.

**Key Words:** Cholecystitis; Gallstones; Choledocholithotomy; Elderly; Post-operative complications

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**Core Tip:** The incidence of gallstone disease is high in octogenarian patients. There are no contraindications in performing cholecystectomy in this population, however, they may be at higher risk of complications. Herein, we will analyze perioperative variables to understand their impact on postoperative courses. Then, we will construct a model in order to help in the selection of patients aged > 80 years who need cholecystectomy.

---

**INTRODUCTION**
Extended life expectancy, coupled with the increased incidence of gallstones with aging, progressively leads to more elderly patients being evaluated for possible surgery for symptomatic gallstones[1,2].

The incidence of gallstones in those aged 80 or over is as high as 38%-53%, and it could increase up to 80% for patients over 90 years of age[3-5]. After an initial episode of biliary colic, 20%-40% of patients will experience recurrent episodes[6,7]. Within one year, 14% of patients will develop acute cholecystitis, 5% biliary acute pancreatitis (BAP) and 5% choledocholithiasis[8,9]. Acute Cholecystitis (AC) is the sixth most common gastrointestinal disease encountered in the emergency department and the second most common cause of hospital admission in the United States[10].

With the aid of modern perioperative care and laparoscopic surgery, patients between 65 and 80 years of age are now thought to have operative risks comparable to the younger population[5]. To date, the outcomes regarding the safety of cholecystectomy performed in older patients are controversial[11-13].

Age itself is one of the critical factors influencing mortality and morbidity after cholecystectomy[14,15]. The greater burden of comorbidities in elderly patients leads to reduced physiological reserve and increased susceptibility to perioperative complications[16]. Outcomes can vary widely, depending on the clinical presentation and whether the procedure is performed electively or as an emergency.

Increasing age has previously been identified as a factor which significantly reduces the likelihood of emergency and elective cholecystectomy being undertaken[12]. One of the reasons quoted for this choice was the reduced life expectancy of this group of patients. The decision about the most appropriate treatment for these patients is always challenging for the surgeon, regardless of the pattern of onset.

The purpose of this study is to assess the risks in terms of morbidity of the octogenarian patients treated with cholecystectomy for symptomatic cholelithiasis (biliary colic, AC, BAP) in order to provide useful data that could help surgeons in the decision process leading to both emergency and elective surgery in this particular population.

**MATERIALS AND METHODS**
A single center retrospective cohort study was conducted on patients who underwent cholecystectomy for symptomatic cholelithiasis between September 2010 and October 2019. Exclusion criteria were age < 80 years and cholecystectomies performed during other surgical procedures. Data were extracted from a retrospective institutional review board-approved database (C.E.ROM. prot. 3238/2019; I.5/263) on
hepatobiliary pancreatic surgery.

Diagnosis of cholelithiasis was performed based on imaging studies: ultrasound (US), computed tomography (CT) and/or magnetic resonance (MR). AC was diagnosed and graded according to the Tokyo Guidelines (TG18)[17]. Postoperative complications were defined according to the Clavien-Dindo classification[18]. The analyzed variables included patients- age, sex, American Society of Anesthesiologists scale (ASA), Body Mass Index (BMI), Charlson comorbidity index (CCI)[19], comorbidity, prior abdominal surgery, laboratory test, radiological imaging, Endoscopic Retrograde Cholangio-Pancreatography (ERCP), diagnosis at admission in urgency; disease- cholelithiasis, cholangitis, AC, TG 18 score; and operation-related- timing, admission surgery interval, surgical approach, associated procedures, operative time, afternoon or night procedure, post-operative complication according to Clavien-Dindo classification, length of hospital stay, supported discharge, mortality.

**Indications and procedures**

Candidates for elective cholecystectomy were those patients with previous history of cholecystitis, biliary colic and/or biliary pancreatitis in the absence of biliary tract lithiasis. In case of choledocholithiasis in the preoperative work-up, in either election or emergency setting patients were referred for preoperative or intraoperative ERCP. Postoperative ERCP was indicated solely in case of choledocholithiasis diagnosed during intraoperative cholangiography in absence of contraindications for endoscopic treatment. The indications for choledocholithotomy were the failure to resolve choledochal lithiasis endoscopically or percutaneously (including by intraoperative Rendez-vous) and Mirizzi’s syndrome type 2.

The laparoscopic approach was performed with the patient placed in the French position. The first 10-12 mm trocar is inserted with an open technique in peri-umbilical area to achieve a 11 mmHg pneumoperitoneum. The other three trocars are positioned under direct vision in the epigastrium (5 mm), 1 Laterally in the right flank (5 mm) and 1 medially in the left flank (10 or 5 mm). In case of open conversion, access with a right subcostal laparotomy was preferred. Antibiotic prophylaxis with 3rd gen cephalosporins was administered in all patients. In case of AC a combination of antibiotics was used and continued based on clinical grounds.

In urgent and elective settings open approach was indicated in high risk patients who had previous gastric surgery or repeated open abdominal surgery; in patients who need a surgical clearance of the common bile duct, in case of anesthetic contraindications to laparoscopy and in case of patient refusal to laparoscopy.

**Statistical analysis**

Data were analyzed using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015). Continuous variables were shown as median and interquartile range (IQR) while categorical data were presented as numbers and percentages. Differences between complicated and uncomplicated patients were analyzed with the Mann–Whitney U test for continuous variables and with the Chi square or Fisher exact tests for the categorical ones.

Logistic regression analyses were performed to investigate the predictors of complications and major complications. The variables who displayed a P < 0.05 at multivariable analysis for Clavien-Dindo < 2 complications were merged in a model and its accuracy was assessed with a receiver operating characteristic (ROC) curve analysis to calculate the Area Under the curve (AUC).

**RESULTS**

Overall, 269 patients (179 urgent vs 90 elective cholecystectomies) were included in the analysis. Patients’ characteristics are shown in Table 1. Overall, 193 (71.7%) patients had a complicated postoperative course (Table 2). ASA score was significantly higher in the patients who had postoperative complications (P = 0.002). Median leukocyte (12850 versus 9300, P = 0.009) and platelets
**Table 1 Patients’ characteristics and their comparison according to the occurrence of postoperative complications**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total cohort (n = 269)</th>
<th>Uncomplicated (n = 76)</th>
<th>Complicated (n = 193)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>83</td>
<td>83 (82.85)</td>
<td>83 (82.87)</td>
<td>0.686</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>126:143</td>
<td>344:200</td>
<td>92:101</td>
<td>0.686</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (0.0)</td>
<td>0</td>
<td>1 (0.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>62 (23.0)</td>
<td>27 (35.5)</td>
<td>35 (38.1)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>179 (66.5)</td>
<td>48 (63.2)</td>
<td>131 (67.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>27 (10.0)</td>
<td>1 (1.3)</td>
<td>26 (13.5)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>24.8 (24-25.1)</td>
<td>26.3 (22.9-28.2)</td>
<td>24.2 (21.1-27.4)</td>
<td>0.062</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>3 (1-4)</td>
<td>3 (2-4)</td>
<td>2 (1-4)</td>
<td>0.145</td>
</tr>
<tr>
<td>Prior upper abdomen surgery</td>
<td>34 (12.6)</td>
<td>11 (32.3)</td>
<td>23 (67.7)</td>
<td>0.548</td>
</tr>
<tr>
<td>Leucocytes (*10⁹/L)</td>
<td>11685 (10520-12957)</td>
<td>9300 (7315-13917)</td>
<td>12850 (8020-18200)</td>
<td>0.009</td>
</tr>
<tr>
<td>Platelets (*10⁹/L)</td>
<td>236 (183-352)</td>
<td>197 (165-262)</td>
<td>272 (189-340)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1.01 (0.58-1.91)</td>
<td>0.82 (0.41-1.53)</td>
<td>1.11 (0.62-2.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>82 (19.7-225)</td>
<td>46.4 (9-184.6)</td>
<td>85.7 (22.2-231.0)</td>
<td>0.135</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>110 (40.9)</td>
<td>28 (36.8)</td>
<td>82 (42.5)</td>
<td>0.412</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>64 (23.8)</td>
<td>12 (15.8)</td>
<td>52 (26.9)</td>
<td>0.057</td>
</tr>
<tr>
<td>Acute cholecystitis Tokyo grade</td>
<td></td>
<td></td>
<td></td>
<td>0.147</td>
</tr>
<tr>
<td>Mild</td>
<td>36 (20.1)</td>
<td>11 (14.5)</td>
<td>25 (13)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>75 (42.0)</td>
<td>18 (23.7)</td>
<td>57 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>68 (37.9)</td>
<td>10 (13.2)</td>
<td>58 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis at admission in urgency</td>
<td></td>
<td></td>
<td></td>
<td>0.374</td>
</tr>
<tr>
<td>A.C.</td>
<td>69 (38.5)</td>
<td>19 (27.6)</td>
<td>50 (72.4)</td>
<td></td>
</tr>
<tr>
<td>A.C. + cholangitis</td>
<td>19 (10.6)</td>
<td>1 (5.2)</td>
<td>18 (94.8)</td>
<td></td>
</tr>
<tr>
<td>A.C. + choleperitonium</td>
<td>25 (14.0)</td>
<td>5 (20)</td>
<td>20 (80)</td>
<td></td>
</tr>
<tr>
<td>A.C. + biliary colic</td>
<td>38 (21.2)</td>
<td>9 (23.7)</td>
<td>29 (76.3)</td>
<td></td>
</tr>
<tr>
<td>A.C. + biliary pancreatitis</td>
<td>28 (15.7)</td>
<td>7 (25)</td>
<td>21 (75)</td>
<td></td>
</tr>
<tr>
<td>Preoperative ERCP</td>
<td>23 (8.6)</td>
<td>11 (14.5)</td>
<td>12 (62)</td>
<td>0.053</td>
</tr>
<tr>
<td>Admission-surgery interval</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
<td>1 (0-3)</td>
<td>0.051</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>100 (73-141)</td>
<td>90 (66-120)</td>
<td>105 (75-150)</td>
<td>0.021</td>
</tr>
<tr>
<td>Surgical approach</td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>53</td>
<td></td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>6 (7.9)</td>
<td>46 (23.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Converted to open</td>
<td>17 (23.4)</td>
<td>32 (16.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative cholangiography</td>
<td>161 (58.9)</td>
<td>35 (46.1)</td>
<td>126 (65.3)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Choledocholithotomy</td>
<td>15 (5.6)</td>
<td>4 (5.3)</td>
<td>11 (5.7)</td>
<td>1</td>
</tr>
<tr>
<td>Transcystic biliary decompression</td>
<td>22 (8.2)</td>
<td>3 (5.9)</td>
<td>19 (9.8)</td>
<td>0.147</td>
</tr>
<tr>
<td>Intraoperative ERCP</td>
<td>28 (10.4)</td>
<td>6 (7.9)</td>
<td>22 (11.4)</td>
<td>0.508</td>
</tr>
<tr>
<td>Afternoon night-procedure</td>
<td>117 (43.5)</td>
<td>24 (31.6)</td>
<td>93 (48.2)</td>
<td>0.014</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>5 (3.8)</td>
<td>3 (2.6)</td>
<td>6 (4.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Supported discharge</td>
<td>47 (17.5)</td>
<td>9 (11.9)</td>
<td>38 (19.7)</td>
<td>0.154</td>
</tr>
</tbody>
</table>

### Table 2 Detailed postoperative complications according to the Clavien Dindo scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Election</th>
<th>Urgency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>54</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Pain</td>
<td>13</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>59</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Mild pancreatitis</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Ileus-delayed flatus</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Septic status</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Urinary problems</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Bile leak</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Cholangitis/retained CBD stone</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary failure</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

CBD: Common bile duct.

(272000 vs 197000, \(P < 0.0001\)) counts at admission were higher in the complicated group. Bilirubin levels were lower in patients who did not have any postoperative complications (0.82 vs 1.11, \(P = 0.011\)). The open approach (23.8% vs 13.0%) was more common in the group who had postoperative complications (\(P = 0.012\)). The complicated group had more intraoperative cholangiography (46.1 vs 65.3%). The uncomplicated group had more cholecystectomies which were performed during afternoon/night (31.6 vs 48.2%, \(P = 0.014\)).

The 9.7% (\(n = 26\)) of complications were grade 3 or 4 according to the Clavien-Dindo classification. The in-hospital mortality rate was 1.5% (\(n = 4\)) while the 90 d mortality rate was 3.9% (\(n = 7\)). The three patients who died after discharge but within 90 days of surgery had had a postoperative course with Clavien-Dindo grade < 3 (Table 2). All cases of postoperative deaths occurred after open or converted urgent cholecystectomy.

At 24 mo follow-up, 195 were alive (85.9%) while 32 (14.1%) died for unrelated causes. For 23 (8.8%) patients last follow-up was at 90 days. At multivariable analysis, performing an intraoperative cholangiography (2.99, 1.43-6.24; \(P = 0.003\)), the diagnosis of cholangitis at admission (12.7, 1.61-100.1; \(P = 0.016\)), platelets count (1.00, 1.00-1.01; \(P = 0.0008\)), the laparoscopic approach (0.10, 0.02-0.46; \(P = 0.003\)) were significantly associated with postoperative complications (Table 3). ASA 4 patients (12.6, 4.27-37.3; \(P < 0.0001\)), performing a choledocholithotomy (10.2, 2.04-51.1; \(P = 0.005\)) and bilirubin levels (1.4, 1.33-1.75; \(P = 0.002\)) were significantly associated with Clavien-Dindo > 2 complications (Table 4) for the whole population.

The ROC curve analysis showed that the model including the three variables to predict Clavien-Dindo > 2 complications had an AUC of 0.79 (0.73-0.85) (Figure 1).
### Table 3 Univariate and multivariate analysis for postoperative complications

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.93-1.08)</td>
<td>0.865</td>
</tr>
<tr>
<td>Sex</td>
<td>0.85 (0.50-1.46)</td>
<td>0.562</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>0.51 (0.28-0.95)</td>
<td>0.027</td>
</tr>
<tr>
<td>3</td>
<td>Ref.</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>9.53 (1.26-72.1)</td>
<td>0.029</td>
</tr>
<tr>
<td>BMI</td>
<td>0.92 (0.85-1.01)</td>
<td>0.073</td>
</tr>
<tr>
<td>CCI</td>
<td>0.82 (0.43-1.60)</td>
<td>0.611</td>
</tr>
<tr>
<td>Prior upper abdomen surgery</td>
<td>0.79 (0.36-1.72)</td>
<td>0.559</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>1.00 (1.00-1.00)</td>
<td>0.009</td>
</tr>
<tr>
<td>Platelets</td>
<td>1.00 (1.00-1.00)</td>
<td>0.013</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.23 (0.97-1.57)</td>
<td>0.081</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>1.00 (0.99-1.00)</td>
<td>0.195</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>1.33 (0.77-2.31)</td>
<td>0.311</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>1.92 (0.96-3.85)</td>
<td>0.065</td>
</tr>
<tr>
<td>Acute cholecystitis Tokyo grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1.55 (0.67-3.35)</td>
<td>0.324</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.19 (1.11-4.32)</td>
<td>0.023</td>
</tr>
<tr>
<td>Severe</td>
<td>4.54 (2.00-10.3)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>3.43 (1.70-6.93)</td>
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</tr>
<tr>
<td>Biliary pancreatitis</td>
<td>1.24 (0.51-3.04)</td>
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<tr>
<td>Gallbladder cancer</td>
<td>1.95 (0.22-17.1)</td>
<td>0.543</td>
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<tr>
<td>Choleperitonium</td>
<td>1.61 (0.58-4.45)</td>
<td>0.36</td>
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<tr>
<td>Cholangitis</td>
<td>12.0 (1.59-89.7)</td>
<td>0.019</td>
</tr>
<tr>
<td>Preoperative ERCP</td>
<td>0.38 (0.16-0.91)</td>
<td>0.03</td>
</tr>
<tr>
<td>Admission-surgery interval</td>
<td>1.04 (0.95-1.14)</td>
<td>0.326</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>0.28 (0.11-0.69)</td>
<td>0.005</td>
</tr>
<tr>
<td>Conversion to open surgery</td>
<td>1.81 (0.37-1.42)</td>
<td>0.354</td>
</tr>
<tr>
<td>Cholecystolithotomy</td>
<td>1.07 (0.33-3.46)</td>
<td>0.914</td>
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<tr>
<td>Intraoperative cholangiography</td>
<td>2.12 (1.23-3.64)</td>
<td>0.007</td>
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<tr>
<td>Intraoperative ERCP</td>
<td>1.47 (0.57-3.78)</td>
<td>0.423</td>
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<tr>
<td>Transcystic biliary decompression</td>
<td>2.57 (0.73-8.95)</td>
<td>0.138</td>
</tr>
<tr>
<td>Afternoon night procedure</td>
<td>2.12 (1.21-3.74)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

ASA: American Society of Anesthesiologists; BMI: Body mass index; ERCP: Endoscopic retrograde cholangio-pancreatography; CCI: Charlson comorbidity index; NA: Not available.

The decision curve analysis is shown in Figure 2. According to the graph, the treating all strategy may be harmful in terms of Clavien-Dindo > 2 complications in patients with threshold probabilities > 13%. The proposed model showed a higher Net benefit than the treating all/none options between threshold probabilities of 11% and 32% of developing a Clavien-Dindo > 2 complication.
### Table 4 Univariate and multivariate analysis for postoperative complications with Clavien-Dindo grade > 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.08 (0.98-1.18)</td>
<td>0.122</td>
</tr>
<tr>
<td>Sex</td>
<td>0.64 (0.30-1.36)</td>
<td>0.255</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.14 (0.02-1.12)</td>
<td>0.064</td>
</tr>
<tr>
<td>3</td>
<td>Ref. 1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6.14 (2.48-15.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>1.12 (1.00-1.26)</td>
<td>0.05</td>
</tr>
<tr>
<td>CCI</td>
<td>1.19 (0.87-4.21)</td>
<td>0.237</td>
</tr>
<tr>
<td>Prior upper abdomen surgery</td>
<td>1.92 (0.72-5.12)</td>
<td>0.193</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>1.00 (1.00-1.01)</td>
<td>0.021</td>
</tr>
<tr>
<td>Platelets</td>
<td>1.00 (1.00-1.00)</td>
<td>0.545</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.37 (0.44-4.26)</td>
<td>0.014</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>1.00 (0.99-1.01)</td>
<td>0.252</td>
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<tr>
<td>Antiplatelet</td>
<td>0.96 (0.44-2.08)</td>
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<tr>
<td>Anticoagulant therapy</td>
<td>2.03 (0.91-4.53)</td>
<td>0.083</td>
</tr>
<tr>
<td>Acute cholecystitis Tokyo grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3.33 (0.71-15.7)</td>
<td>0.128</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.38 (0.86-13.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Severe</td>
<td>8.02 (2.21-29.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>0.79 (0.33-1.87)</td>
<td>0.599</td>
</tr>
<tr>
<td>Biliary pancreatitis</td>
<td>0.26 (0.03-1.98)</td>
<td>0.194</td>
</tr>
<tr>
<td>Choleperitoneum</td>
<td>2.89 (1.05-7.95)</td>
<td>0.039</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>1.37 (0.44-4.26)</td>
<td>0.579</td>
</tr>
<tr>
<td>Preoperative ERCP</td>
<td>0.74 (0.16-3.33)</td>
<td>0.696</td>
</tr>
<tr>
<td>Admission-surgery interval</td>
<td>1.05 (0.99-1.11)</td>
<td>0.115</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>0.18 (0.08-0.40)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Conversion to open surgery</td>
<td>1.81 (0.75-4.35)</td>
<td>0.185</td>
</tr>
<tr>
<td>Cholecystolithotomy</td>
<td>4.58 (1.45-14.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Transcystic biliary decompression</td>
<td>5.81 (2.20-15.4)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Intraoperative cholangiography</td>
<td>0.86 (0.40-1.86)</td>
<td>0.706</td>
</tr>
<tr>
<td>Intraoperative ERCP</td>
<td>1.38 (0.44-4.28)</td>
<td>0.579</td>
</tr>
<tr>
<td>Afternoon night procedure</td>
<td>1.82 (0.84-3.91)</td>
<td>0.126</td>
</tr>
</tbody>
</table>

ASA: American Society of Anesthesiologists; BMI: Body mass index; ERCP: Endoscopic retrograde cholangio-pancreatography; CCI: Charlson comorbidity index; NA: Not available.

### DISCUSSION

Even though gallstones increase with aging, older patients are less likely to undergo cholecystectomy[1, 22]. In fact, it has been estimated that less than a quarter of elderly patients who meet the criteria for elective cholecystectomy undergo surgery[1,22]. This is because increasing age is a negative predictor after cholecystectomy, due to the higher perceived surgical risks, especially after hospitalization for
complications of gallstones[1]. In this clinical arena, the availability of a tool to support the surgeon in his decision making is of utmost importance.

Cholecystectomy for symptomatic gallstone disease is associated with a high postoperative complication rate in octogenarians. However, it must be highlighted that only 9.7% of patients had a severe complication, indicating that cholecystectomy could remain a treatment option in this population. In line with this assumption, the NICE 2014[23] and TG18[17] guidelines did not suggest an age cut-off to surgically treat symptomatic gallstone disease or cholecystitis.

Other reports showed similar high morbidity rates ranging between 14.7% and 51%[24-27]. Only 3 studies with populations with similar characteristics reported complications graded according to the Clavien-Dindo classification and all found that the majority of complications were Clavien-Dindo grade 1-2 characteristics [28-30].

The feasibility of cholecystectomy in octogenarians was evaluated in different studies that confirmed its safety, but in the investigated “all comers” groups the surgical treatment in an elective setting always represented more than half of the cases[28]. Differently, the population analyzed in this study was characterized by a limited number of patients (33.5%) treated electively with cholecystectomy.

In addition, according to our analysis, cholecystectomy seemed to be associated with acceptable safety parameters in moderate-severe acute cholecystitis. As such, 90 d mortality in our cohort was 2.6%. This is similar to what has been reported by the two largest single-center studies which showed
D’Acapito F et al. Criteria for selecting elderly for cholecystectomy

in-hospital mortality ranging between 4% to 4.8%[28,31]. This was also confirmed by a recent systematic review comparing the outcomes of patients with 65-79 vs ≥ 80 years which showed a mortality rate of 0%-4.6% in the older age group[5].

A severely complicated postoperative course may have a dramatic impact on the elderly patients who may not return to their previous level of activity[32].

Our analysis could find those factors which could help in predicting those patients at risk of having a severely complicated postoperative course.

According to the decision curve analysis our model may be of use in selecting those elderly patients at the lowest risk of severe complications for whom cholecystectomy should be performed.

We found that ASA 4 patients with elevated bilirubin levels and in need of choledocholithotomy had the highest risk of developing a Clavien-Dindo > 2 complication. The risk of a Clavien-Dindo > 2 complication was nearly 80% for this subgroup of patients.

This may indicate the need of considering alternative non-operative approaches for this subgroup of patients, preferring endoscopic/percutaneous options.

Our paper appears to be the first in the literature to document a statistically significant correlation between the use of choledocholithotomy and complications.[33,34] This may be due to the fact that our analysis focused on a very select population of patients with > 80 years of age. This finding may suggest considering a surgical-endoscopic ‘rendez-vous’ procedure as an alternative to choledocholithotomy [35]. However, additional studies on this approach on the oldest-old populations are warranted to confirm this hypothesis.

The limitations of this study are linked to its retrospective nature whose outcomes may be confounded by selection bias. As such, the cohort may include the fittest patients, for whom a definitive treatment like cholecystectomy may not represent a major risk. In addition, we could not provide data on frailty which may be another factor to consider when dealing with the oldest-old patients. This might have helped in creating an even more accurate model in predicting patients at risk for severe postoperative complications following cholecystectomy for gallstone disease. Finally, since the study is based on a surgical database, we could not consider those patients treated only with percutaneous/endoscopic procedures which might be considered a treatment option for a subpopulation of octogenarians.

CONCLUSION

ASA 4 patients with higher levels of bilirubin at admission who may need a choledocholithotomy are at the highest risk of a severely complicated postoperative course. These factors should be included in the decision-making process in defining the ideal elderly patients to be submitted to cholecystectomy for cholelithiasis in either an emergency or elective setting.

ARTICLE HIGHLIGHTS

Research background
Incidence of gallstones in those aged ≥ 80 years is as high as 38%-53%. This population is at higher risk of complication following cholecystectomy with postoperative morbidity rates up to over 50%.

Research motivation
The decision-making process for selecting patients undergoing surgery is challenging. A model which can identify the patients at the highest risk would be helpful for selecting the ideal candidate for cholecystectomy in a population aged ≥ 80 years.

Research objectives
The purpose of this study is to assess the perioperative risk of the octogenarian patients treated with cholecystectomy and to create a model that could help surgeons in the decision-making process leading to surgery in this population.

Research methods
An institutional review board-approved database was exploited to analyze all patients aged ≥ 80 years who had cholecystectomy between 2010 and 2019. Logistic regression analysis was performed to identify the perioperative variables associated with postoperative complications. Then a model was created and tested to predict severe postoperative morbidity.

Research results
Clavien-Dindo complications rate > 2 was 9.7%. A model including American Society of Anesthesi-
ologists (ASA) scale 4 patients, performing a choledocholithotomy and bilirubin levels were associated with Clavien-Dindo > 2 complications ($P < 0.001$). The decision curve analysis showed that the proposed model had a higher net benefit than the treating all/none options between threshold probabilities of 11% and 32% of developing a severe complication.

**Research conclusions**

Patients with ASA 4, higher level of bilirubin and need of choledocholithotomy are at the highest risk of a severely complicated postoperative course.

**Research perspectives**

Future analyses confirming these results should focus on alternative endoscopic or percutaneous treatments that may be more suitable treatments for this subgroup of octogenarian.

**ACKNOWLEDGEMENTS**

Thanks to Dr. Angelo Paolo Ciarrocchi for revising the language editing.

**FOOTNOTES**

**Author contributions:** All authors contributed to the study conception and design; Material preparation, data collection and analysis were performed by D’Acapito F, Solaini L, Di Pietrantonio D, Tauceri F, Mirarchi MT, Antelmi E, Flamini F, Amato A, Framarini M and Ercolani G; The first draft of the manuscript was written by D’Acapito F, Solaini L and Ercolani G; All authors commented on previous versions of the manuscript, read and approved the final manuscript; and D’Acapito F and Solaini L contributed equally to this paper.

**Institutional review board statement:** The study was reviewed and approved by the Ethics Committee of ROMAGNA CEROM (10/04/2019) (Approval No. 3238/2019 L5/263).

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Data sharing statement:** The datasets generated during and/or analyzed during the current study are not publicly available due privacy policies but are available from the corresponding author on reasonable request.

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**S-Editor:** Ma YJ
**L-Editor:** A
**P-Editor:** Yuan YY

**REFERENCES**


4. **Ekici U**, Yilmaz S, Tatli F. Comparative Analysis of Laparoscopic Cholecystectomy Performed in the Elderly and Younger


26 Lupinacci RM, Nadal LR, Rego RE, Dias AR, Marcari RS, Lupinacci RA, Farah JF. Surgical management of gallbladder disease in the very elderly: are we operating them at the right time? Eur J Gastroenterol Hepatol 2013; 25: 380-384 [PMID: 23169310 DOI: 10.1097/MEG.0b013e32835b7124]


Clinical Trials Study

Computed tomography combined with gastroscopy for assessment of pancreatic segmental portal hypertension

Yu-Li Wang, Han-Wen Zhang, Fan Lin

**Abstract**

**BACKGROUND**

Pancreatic segmental portal hypertension (PSPH) is the only type of portal hypertension that can be completely cured. However, it can easily cause varicose veins in the esophagus and stomach and hemorrhage in the digestive tract.

**AIM**

To explore the application of computed tomography (CT) to examine the characteristics of PSPH and assess the risk level.

**METHODS**

This was a retrospective analysis of CT images of 22 patients diagnosed with PSPH at our center. Spearman correlation analysis was performed using the range of esophageal and gastric varices (measured by the vertical gastric wall), the ratio of the width of the splenic portal vein to that of the compression site (S/C ratio), the degree of splenomegaly, and the stage determined by gastroscopy. This study examined whether patients experienced gastrointestinal bleeding within 2 wk and combined CT and gastroscopy to explore the connection between bleeding and CT findings.

**RESULTS**

The range of esophageal and gastric varices showed the best correlation in the diagnosis of PSPH ($P < 0.001$), and the S/C ratio ($P = 0.007$) was correlated with the degree of splenomegaly ($P = 0.021$) and PSPH ($P < 0.05$). This study revealed that male patients were more likely than females to progress to grade 2 or grade 3 as determined by gastroscopy. CT demonstrated excellent performance, with an area under the curve of 0.879.

**CONCLUSION**
CT can be used to effectively analyze the imaging signs of PSPH, and CT combined with gastroscopy can effectively predict the risk level of gastrointestinal bleeding.

Key Words: Computed tomography; Pancreatic segmental portal hypertension; esophageal and gastric varices; Gastrointestinal bleeding; Curable portal hypertension

Core Tip: This is a detailed clinical imaging study (computed tomography, CT) of pancreatic segmental portal hypertension (PSPH), the only curable form of portal hypertension. CT is of great significance in the diagnosis and treatment of PSPH.

INTRODUCTION

Pancreatic segmental portal hypertension (PSPH) is a rare regional condition, accounting for only 8% of extrabiliary portal hypertension cases[1]. PSPH is usually caused by pancreatic tumors, pancreatitis, and IgG4-related diseases that cause pancreatic vein compression. Clinically, it manifests as regional portal hypertension on the left side; usually, the right portal system is not significantly affected[2]. At the same time, it is now the only curable form of portal hypertension. However, if PSPH is not detected early, continuous compression of the pancreatic veins will cause esophageal and gastric varices, which may lead to hemorrhage in the gastrointestinal tract. In severe cases, hemorrhagic shock or death may occur. Therefore, it is essential to diagnose PSPH as soon as possible and assess whether there is a tendency for gastrointestinal bleeding[3].

Because other underlying diseases of the pancreas usually cause this type of disease, it can generally be cured by removing the underlying disease[4,5]. This approach ignores the risk of gastrointestinal bleeding in this type of patient. Clinicians usually only focus on curing the underlying disease, and iatrogenic secondary injuries after tumor resection or pancreatitis treatment may also cause a continuous increase in the pressure of the already narrowed pancreatic veins, leading to an increased risk of gastrointestinal bleeding[6-8]. At the same time, splenomegaly or hypersplenism caused by PSPH can also cause increased blood cell destruction and decreased resistance. Therefore, this disease is receiving increasing attention in clinical practice[9].

The diagnostic criteria for this type of disease are as follows: (1) A history of primary pancreatic disease; (2) No history of liver cirrhosis, blood system disease, or schistosomiasis disease and normal liver function; (3) Splenomegaly or hypersplenism; (4) Doppler ultrasound results showing that the portal vein is not wide [only the splenic vein is obstructed with or without widening of the splenic portal vein, and there are regional varicose veins on the left side (usually esophageal and gastric varices)]; and (5) varicose vascular masses observable under gastroscopy. PSPH can be diagnosed when three of the above five criteria are satisfied[10]. Among the current diagnostic criteria, criteria (1) and (2) are met by almost all diagnosed patients. However, splenomegaly does not appear in all patients. Gastroscopy can only elucidate varicose veins that have compressed the fundus or esophagus. Pancreatic effusion or gas will also obscure the site analyzed by Doppler ultrasound. Therefore, the diagnosis of varicose veins under gastroscopy combined with the clinical history can usually be used to diagnose the disease.

Due to the relatively rare nature of this type of disease, clear computed tomography (CT) findings of this type of disease have not yet been determined. However, CT has apparent advantages over ultrasound and gastroscopy. It is not affected by gas and can reflect deeper varicose veins. In addition, contrast enhanced CT during the portal phase can also facilitate an excellent preliminary judgment regarding stenosis of the splenic portal vein. It can also be used to evaluate enlargement of the spleen. Moreover, CT is more convenient than digital subtraction angiography and can reflect the initial vascular condition[11]. In this study, CT signs were combined with the manifestations of gastric fundal and esophageal varices to explore the appearance of PSPH on CT and the risk of gastrointestinal bleeding.
MATERIALS AND METHODS

Patients
CT images of 22 patients who had clinically confirmed PSPH from 2007 to 2021 at our center were collected. Among them, 14 were men and 8 were women, aged 26-69 years old. These patients had a history of pancreatic or pancreatic area disease and had complete gastroscopic image data. The current study was approved by the Institutional Review Board, and the requirement for informed consent was waived (Clinical Research Ethics Committee of Shenzhen Second People's Hospital, approval ID: 20211108009).

CT parameters
All patients were examined using a 32-section CT system (Siemens Healthcare Sector, Germany). Before the CT examination, the patient fasted for 4–6 h without intramuscular antispasmodic drug injection or oral contrast agent administration. The scanning range was from the top of the diaphragm to the mid-abdominal level. The scanning parameters used were as follows: Collimator width, 64 mm × 0.625 mm; tube voltage, 100 kVP; tube current, automatically controlled at 85-150 mA; and X-ray tube rotation speed, 0.5 s/cycle. The reconstruction layer thickness was 2.0 mm, and the layer spacing was 0 mm. The enhanced scan was performed using contrast agent intelligent tracking threshold trigger technology. The trigger point was set in the abdominal aortic lumen at the celiac trunk. The trigger threshold was 120 HU. The venous phase started to be collected 30 s after the end of the arterial-phase scan. Iopromide (iodine concentration, 350 mg/mL) was used as the contrast agent at a dose of 1.2 mL/kg, and the injection rate was 3.0 mL/s.

Image analysis
Because the portal phase can better reflect the pancreatic veins, the enhanced portal phase of the CT images of the above PSPH patients was analyzed. Three senior doctors interpreted the images and measured the diameter of the splenic vein in the compressed area and the diameter of the splenic vein at the splenic hilum. The rib unit was measured at the largest level of the spleen, and the largest side of the varicose vein was measured. The vertical distance from the outermost edge to the stomach wall was taken as the range of varicose veins (Figure 1, patient 1). To reduce differences between men and women and individual patients, the splenic meridian was not directly measured; instead, the number of rib units was used. The degree of vascular stenosis was determined by the ratio of the diameter of the splenic portal vein to that at the site of splenic vein compression (S/C).

At the same time, we combined the findings from the abovementioned analyses with those of the gastroscopy report from the Department of Gastroscopy to classify these PSPH patients with esophageal varices by gastroscopy, as follows: Grade 1: The varicose veins are straight or slightly tortuous, and there is no "red sign"; grade 2: The veins are straight or somewhat tortuous with the red sign or exhibit a snake-like tortuosity without the red sign; and grade 3 (G3): The varicose veins are serpentine with the red sign or the vascular abnormalities are beaded and nodular and exhibit a tumor-like bulge accompanied (or not) by the red sign. The red sign represents a high risk of bleeding in the digestive tract[12]. The patients were followed, and whether bleeding occurred within 2 wk after the scan was recorded.

Statistical analysis
The above patient clinical information and imaging measurement information are presented in Table 1. SPSS 19.0 (SPSS v. 19, Chicago, Illinois) was used for statistical analyses. Because the data did not conform to a normal distribution, the Spearman test combined with the stage diagnosed by gastroscopy were employed to compare and test various measurement parameters. \( P < 0.05 \) indicated statistical significance. All statistical graphs were created using GraphPad Prism 7 (Prism 7, La Jolla, California).

According to whether bleeding occurred within 2 wk, the patients were divided into a bleeding group (\( n = 8 \)) and a nonbleeding group (\( n = 14 \)). The Mann–Whitney U test was used to compare continuous variables between the bleeding and nonbleeding groups. \( P \) value < 0.05 was considered statistically significant. All patients' continuous and categorical variables are represented as the mean ± SD and \( n (\%) \), respectively. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic capability of CT, including calculation of the area under the curve (AUC) and 95% confidence interval.

RESULTS
The results of Spearman's test are shown in Table 2. The parameters with the correlation coefficient from high to low were the range of varicose veins (correlation coefficient = 0.873, \( P < 0.001 \)), S/C ratio (correlation coefficient = 0.518, \( P = 0.007 \)), and number of rib units (correlation coefficient = 0.436, \( P = 0.021 \)). The range of varicose veins showed the strongest correlation with the gastroscopic grade. In
Table 1 Patient information and measurement list

<table>
<thead>
<tr>
<th>Patient ID (n = 22)</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical history</th>
<th>Splenic portal vein width (mm)</th>
<th>Compression area vein width (mm)</th>
<th>S/C ratio</th>
<th>Varicose vein range (mm)</th>
<th>Rib unit</th>
<th>Gastroscopy grade</th>
<th>Gastrointestinal bleeding within 2 wk</th>
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</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Male</td>
<td>26</td>
<td>CP</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>50</td>
<td>7</td>
<td>G3</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Male</td>
<td>58</td>
<td>AP</td>
<td>6</td>
<td>2.5</td>
<td>2.4</td>
<td>36</td>
<td>9</td>
<td>G2</td>
<td>No</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Male</td>
<td>57</td>
<td>CP</td>
<td>4.5</td>
<td>2</td>
<td>2.25</td>
<td>36</td>
<td>7.5</td>
<td>G3</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Male</td>
<td>53</td>
<td>PTC</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>37</td>
<td>7.5</td>
<td>G3</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Male</td>
<td>63</td>
<td>PTC</td>
<td>4</td>
<td>3</td>
<td>1.333</td>
<td>21</td>
<td>5</td>
<td>G1</td>
<td>No</td>
</tr>
<tr>
<td>Patient 6</td>
<td>Male</td>
<td>34</td>
<td>CP</td>
<td>6.5</td>
<td>4.5</td>
<td>1.444</td>
<td>24</td>
<td>5.5</td>
<td>G2</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 7</td>
<td>Male</td>
<td>67</td>
<td>PBC</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>10</td>
<td>7</td>
<td>G1</td>
<td>No</td>
</tr>
<tr>
<td>Patient 8</td>
<td>Male</td>
<td>69</td>
<td>PTC</td>
<td>5</td>
<td>6</td>
<td>0.833</td>
<td>16</td>
<td>6</td>
<td>G2</td>
<td>No</td>
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<tr>
<td>Patient 9</td>
<td>Female</td>
<td>56</td>
<td>PBC</td>
<td>5</td>
<td>2</td>
<td>2.5</td>
<td>5</td>
<td>5</td>
<td>G1</td>
<td>No</td>
</tr>
<tr>
<td>Patient 10</td>
<td>Male</td>
<td>65</td>
<td>PHC</td>
<td>6</td>
<td>4</td>
<td>1.5</td>
<td>11</td>
<td>8</td>
<td>G2</td>
<td>No</td>
</tr>
<tr>
<td>Patient 11</td>
<td>Female</td>
<td>67</td>
<td>PHC</td>
<td>4</td>
<td>3</td>
<td>1.333</td>
<td>5</td>
<td>5</td>
<td>G1</td>
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<tr>
<td>Patient 12</td>
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<td>60</td>
<td>PHC</td>
<td>5</td>
<td>3</td>
<td>1.667</td>
<td>26</td>
<td>8</td>
<td>G2</td>
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</tr>
<tr>
<td>Patient 13</td>
<td>Female</td>
<td>55</td>
<td>PTC</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td>G1</td>
<td>No</td>
</tr>
<tr>
<td>Patient 14</td>
<td>Male</td>
<td>63</td>
<td>PTC</td>
<td>8</td>
<td>2</td>
<td>4</td>
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<td>7</td>
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<td>No</td>
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<tr>
<td>Patient 15</td>
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<td>40</td>
<td>PTC</td>
<td>6</td>
<td>5</td>
<td>1.2</td>
<td>6</td>
<td>8</td>
<td>G1</td>
<td>No</td>
</tr>
<tr>
<td>Patient 16</td>
<td>Male</td>
<td>27</td>
<td>CP</td>
<td>7</td>
<td>4</td>
<td>1.75</td>
<td>28</td>
<td>8</td>
<td>G2</td>
<td>No</td>
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<tr>
<td>Patient 17</td>
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<td>66</td>
<td>PHC</td>
<td>7</td>
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<td>0.636</td>
<td>2</td>
<td>7</td>
<td>G1</td>
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<tr>
<td>Patient 18</td>
<td>Male</td>
<td>68</td>
<td>PBC</td>
<td>5</td>
<td>3</td>
<td>1.667</td>
<td>16</td>
<td>7</td>
<td>G2</td>
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<tr>
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<td>50</td>
<td>PHC</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>33</td>
<td>7</td>
<td>G2</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 20</td>
<td>Female</td>
<td>52</td>
<td>PBC</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>15</td>
<td>7</td>
<td>G1</td>
<td>Yes</td>
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<tr>
<td>Patient 21</td>
<td>Male</td>
<td>38</td>
<td>CP</td>
<td>7</td>
<td>1.5</td>
<td>4.667</td>
<td>38</td>
<td>7</td>
<td>G3</td>
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</tr>
<tr>
<td>Patient 22</td>
<td>Male</td>
<td>58</td>
<td>IgG4-P</td>
<td>7</td>
<td>2</td>
<td>3.5</td>
<td>32</td>
<td>8</td>
<td>G3</td>
<td>Yes</td>
</tr>
</tbody>
</table>

S/C ratio: The ratio of the splenic portal vein width to the compression area vein width; CP: Chronic pancreatitis; AP: Acute pancreatitis; PHC: Pancreatic head cancer; PBC: Pancreatic body cancer; PTC: Pancreatic tail cancer; IgG4-P: IgG4 pancreatitis.

Table 2 Spearman correlation analysis of gastroscopic grade and various factors

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age</th>
<th>Splenic portal vein width</th>
<th>Compression area vein width</th>
<th>S/C ratio</th>
<th>Varicose vein range</th>
<th>Rib unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation coefficient</td>
<td>0.757</td>
<td>-0.296</td>
<td>0.330</td>
<td>-0.405</td>
<td>0.518</td>
<td>0.873</td>
<td>0.436</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>0.091</td>
<td>0.067</td>
<td>0.031</td>
<td>0.007</td>
<td>&lt; 0.001</td>
<td>0.021</td>
</tr>
</tbody>
</table>

P < 0.05 indicates statistical significance. When the correlation coefficient is closer to 1, it means that the correlation of the parameter is stronger. Negative values represent a negative correlation. S/C ratio: The ratio of the splenic portal vein width to the compression area vein width.

addition to the main measurement parameters, the width of the compression site also showed a statistically significant (P = 0.031) negative correlation; that is, the narrower the width, the higher the grade of esophageal varices. Figure 2 shows a box diagram with the three main measurement value distributions at different levels under gastroscopy. Surprisingly, the results also showed that the severity of esophageal varices in male patients with PSPH was usually higher than that in female patients, which had a statistically significant difference (P < 0.001). However, there was no statistically significant difference based on patient age.
Wang YL et al. CT combined with gastroscopy for PSPH assessment

Figure 1 A 42-year-old male with a history of chronic pancreatitis (patient 1). A: A tortuous vascular shadow was observed in the upper esophagus and gastric fundus area on plain computed tomography (CT); B: The tortuous venous cluster was more evident on enhanced CT, and the longest diameter (red line) measured was 50 mm (perpendicular to the gastric wall, orange line); C: On gastroscopy, obvious tortuosity was observed in the inferior fundus veins (blue arrow); D: On gastroscopy, the blood vessels of the gastric body appeared as beaded, tumor-like bulges (G3, blue arrow).

Figure 2 Box diagram of each parameter graded by gastroscopy. A: Varicose vein range (mm); B: S/C ratio; C: Spleen size (number of rib units).

Predictive value of CT for bleeding
The Mann–Whitney U test showed that the S/C ratio, range of varicose veins, and gastroscopic grade were significant independent predictors of bleeding (Table 3). The ROC curve analysis showed excellent performance, with an AUC of 0.879 for the varicose vein range and 0.844 for the gastroscopic grade (Figure 3).

DISCUSSION
PSPH, as a rare type of portal hypertension, has vital clinical significance. Nevertheless, it is easy to ignore the existence of this disease because of the excessive emphasis on the original condition in diagnostic images[13]. However, gastroscopy usually delays the diagnosis of such diseases when the imaging findings are ignored, for example, as occurred in the patient (Figure 4) who had IgG4-related pancreatitis. Gastroscopy was only used 4 d after admission, and the typical "red sign" had already appeared. The patient developed massive gastrointestinal bleeding within 24 h. Although he was rescued in time, the prognosis was poor. While paying attention to the primary disease, physicians also need to evaluate whether the patient has excessive portal hypertension and the degree of splenic vein compression in the pancreatic area[14].

This study found that the degree of varicose veins under gastroscopy correlated with the maximum vertical measurement of esophageal varices under CT. The S/C ratio was also positively associated with the size of the spleen. Initially, we had various ideas for measuring the meridian, such as a second graded measurement of the varicose veins. In addition to calculating the vertical meridian of the largest plane, judgment of the density of varicose veins (through the number of cross-sections of the vessel on this plane) can be performed. However, such measurements have certain drawbacks. In some patients, although the degree of varicosity may be more significant, the blood vessel diameter may be smaller; other patients may show a more substantial degree of varicosity, but the vessel diameter may be larger. This results in the inability to perform practical grading measurements on patients, and the clinical operation is more complicated, requiring much more time for evaluation. Thus, this situation may be dangerous for emergency patients[15].
### Table 3 Clinical characteristics, imaging characteristics, and computed tomography measurement values in different bleeding and non-bleeding groups (Mann-Whitney U test)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bleeding (n = 8)</th>
<th>Non-bleeding (n = 14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>46.000 ± 11.796</td>
<td>58.860 ± 11.890</td>
<td>0.024</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.079</td>
</tr>
<tr>
<td>Male</td>
<td>7 (50%)</td>
<td>7 (50%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1 (12.5%)</td>
<td>7 (87.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Gastroscopic grade</strong></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>G1</td>
<td>1 (12.5%)</td>
<td>7 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>2 (22.2%)</td>
<td>7 (77.8%)</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>5 (100%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>CT measurement value</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenic portal vein width (mm)</td>
<td>6.571 ± 0.790</td>
<td>5.571 ± 1.223</td>
<td>0.245</td>
</tr>
<tr>
<td>Compression area vein width (mm)</td>
<td>2.375 ± 0.954</td>
<td>3.964 ± 2.308</td>
<td>0.074</td>
</tr>
<tr>
<td>S/C ratio</td>
<td>2.858 ± 0.989</td>
<td>1.701 ± 0.852</td>
<td>0.011</td>
</tr>
<tr>
<td>Varicose vein range (mm)</td>
<td>33.125 ± 10.316</td>
<td>15.286 ± 10.462</td>
<td>0.002</td>
</tr>
<tr>
<td>Rib unit</td>
<td>7.063 ± 0.729</td>
<td>6.857 ± 1.292</td>
<td>0.668</td>
</tr>
</tbody>
</table>

*P* < 0.05 indicates statistical significance. Values are the mean ± SD. G1: Grade 1; G2: Grade 2; G3: Grade 3; CT: Computed tomography.

Figure 3 Receiver operating characteristic curves of computed tomography measurements and gastroscopy stage for predicting bleeding risk in patients with pancreatic segmental portal hypertension.

Compared with the range of varicose vessels, the S/C ratio shows a specific correlation. However, if the splenic vein is significantly compressed and interrupted, this measurement method will be difficult to perform. If enhanced CT can indicate the interruption point of the splenic vein in the portal phase, targeted diagnosis and treatment will be necessary to relieve the compression of the lesion. Although the size of the spleen is related to a certain degree, it is greatly affected by time. Splenic enlargement can also be resolved after relieving compression to avoid resection[16]. The early stage of PSPH usually manifests as esophageal and gastric varices. Additionally, this study found a higher grade of varicose veins in male patients than female patients. This may be related to men's alcohol consumption and women's sensitivity to pain, which allows early detection. This view has been confirmed in a study of acute pancreatitis[17,18].

DOI: 10.12998/wjcc.v10.i24.8568  Copyright ©The Author(s) 2022.
All patients in this study had underlying pancreatic disease. Vigilance regarding the occurrence of PSPH is required in such patients. Most studies regarding PSPH assessed by CT are rare case reports, and there has been no detailed research or consensus yet[19]. CT studies by Swan Specchi and Giovanna Bertolini in animal models have shown that esophageal variances often occur in the collateral circulation established by esophageal fundus veins, such as the left gastric vein and the left gastroepiploic vein, which CT can better visualize to show the collateral circulation in PSPH[20]. We recommend that for patients with underlying pancreatic disease, plain and enhanced CT scans should be used to make a preliminary judgment of the PSPH severity. We propose the use of the “banyan tree root” sign (Figure 5) to identify high-risk PSPH. When there is a banyan tree root-like change, clinicians should be highly vigilant regarding the risk of gastrointestinal bleeding; such patients need to undergo emergency gastroscopy to prevent a poor prognosis.

This study found that CT is a powerful supplement to gastroscopy. Although CT and gastroscopy alone provide excellent results when applied to detect PSPH-related bleeding, it is necessary to be alert to the occurrence of exceptional circumstances. For example, if the scope of gastric esophageal varices is enormous but the gastroscopic grade has not yet reached G3, the physician should still be alert for gastrointestinal bleeding. In patients with abdominal pain after pancreatic disease, even conventional CT scans can initially be used to determine whether there are esophageal varices in the fundus of the stomach. Enhanced CT can better assess the location and extent of stenosis. At the same time, gastroscopy is an invasive examination, and CT examination can be more convenient for judging the prognosis of pancreatic patients.

PSPH is relatively rare in clinical practice, and the number of patients included in this study is relatively small, which dramatically restricts the related statistical analysis. Although this study reached a somewhat preliminary conclusion, more cases are required to explore the role of imaging in this type of disease and reach a more accurate conclusion. The clinical judgment of PSPH is usually an exclusive diagnosis; that is, the regional portal hypertension of left-sided portal hypertension is caused only by compression of the pancreatic veins[21]. As PSPH is the only form of portal hypertension that can be cured entirely, excellent attention in clinical and imaging studies is required to better treat and improve the prognosis of PSPH patients.

This study has several limitations: (1) Since this was a small sample study, the results may be greatly influenced by individuals. The inclusion of more samples would further improve the credibility of this study; and (2) With a sufficient number of samples, a more reliable diagnostic model could be established, and a subset of patient data could be entered into the model to verify the model’s reliability.
CONCLUSION
Measuring gastric and esophageal varices and assessing the degree of splenic vein stenosis at the site of compression on CT combined with gastroscopy can effectively predict bleeding in patients with PSPH. CT is of great significance in the diagnosis and treatment of PSPH.

ARTICLE HIGHLIGHTS

Research background
Pancreatic segmental portal hypertension (PSPH) is the only type of portal hypertension that can be completely cured.

Research motivation
PSPH can easily cause varicose veins in the esophagus and stomach and hemorrhage in the digestive tract.

Research objectives
To explore the application of computed tomography (CT) to examine the characteristics of PSPH and assess the risk level.

Research methods
This was a retrospective analysis of CT images of 22 patients diagnosed with PSPH at our center. Spearman correlation analysis was performed using the range of esophageal and gastric varices (measured by the vertical gastric wall), the ratio of the width of the splenic portal vein to that of the compression site (S/C ratio), the degree of splenomegaly, and the stage determined by gastroscopy. The study examined whether patients experienced gastrointestinal bleeding within 2 wk and combined CT and gastroscopy to explore the connection between bleeding and CT findings.

Research results
The range of esophageal and gastric varices showed the best correlation in the diagnosis of PSPH ($P < 0.001$), and the S/C ratio ($P = 0.007$) was correlated with the degree of splenomegaly ($P = 0.021$) and PSPH ($P < 0.05$). The study revealed that male patients were more likely than females to progress to grade 2 or grade 3 as determined by gastroscopy. CT imaging demonstrated excellent performance, with an area under the curve of 0.879.

Research conclusions
CT can be used to effectively analyze the imaging signs of PSPH, and CT combined with gastroscopy can effectively predict the risk level of gastrointestinal bleeding.

Research perspectives
This was a detailed clinical imaging study (computed tomography, CT) of PSPH, the only curable form of portal hypertension. CT is of great significance in diagnosing and treating PSPH.
ACKNOWLEDGEMENTS

Thanks to Ms. Si-Ling Gu for her help in this research.

FOOTNOTES

Author contributions: Zhang HW contributed to the conception of the study; Lin F performed the data analyses and wrote the manuscript; Wang YL helped perform the analysis with constructive discussions.

Supported by: Shenzhen Science and Technology Plan Project, No. JCYJ20180228163333734.

Institutional review board statement: This study was approved by the local ethics committee (Ethics Committee of Shenzhen Second People's Hospital), No. 20211108009.

Clinical trial registration statement: This study is registered at Ethics Committee of Shenzhen Second People's Hospital. This study is registered at Chinese Clinical Trial Registry. The registration identification number is ChiCTR2100049175.

Informed consent statement: This study included completely anonymous data, and the ethics committee agreed to waive the patient's right of informed consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: All data used in this study are included in the article.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

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Country/Territory of origin: China

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REFERENCES


Psychological needs of parents of children with complicated congenital heart disease after admitting to pediatric intensive care unit: A questionnaire study

Ji-Hua Zhu, Chen-Di Jin, Xiao-Min Tang

BACKGROUND
Parents of children with complicated congenital heart disease (CHD) have different needs after surgery. Little literature reports the impact factors for psychological needs of parents of children with complicated CHD.

AIM
To investigate the status quo of the needs of parents of children after surgery for complex CHD, and analyze the influencing factors, in order to provide a theoretical basis for formulating corresponding nursing countermeasures.

METHODS
A modified Chinese version of the Critical Care Family Needs Inventory (M-CCFNI) was used to select 200 parents of children with complex CHD after surgery within 72 h after admission to the intensive care unit in our hospital to conduct an online questionnaire survey. The aim was to understand the needs of parents in relation to the following five aspects: The support from medical staff, comfort of the parents themselves, the acquisition of information, their closeness to the children, and assurance of the child’s condition.

RESULTS
Parents of children with complex CHD had a higher degree of demand, especially in terms of condition assurance, acquisition of information, and closeness to the children. The age, education level, and residence of the parents were related to the five dimensions of the needs of parents of children with complex CHD who had undergone surgery.
CONCLUSION
In practice, nurses should formulate corresponding nursing strategies based on the different cultural and social backgrounds of parents of children after complex CHD surgery to meet their different needs, and improve satisfaction. These findings provide a theoretical basis for constructing a family participatory nursing model for children in the intensive care unit in the future.

Key Words: Congenital heart disease; Family participation; Psychological needs; Nursing model; Pediatric intensive care unit

INTRODUCTION
According to relevant data[1-3], approximately 150000-200000 newborns in China suffer from congenital heart disease (CHD) each year, accounting for about 0.8% of all live births. CHD is the most common birth defect in China, and there are more and more complicated CHDs with any combination of “ventricular septal defect, atrial septal defect, patent ductus arteriosus, and simple pulmonary stenosis”. Studies have shown that due to improvements in medical standards, surgical correction is the only way to cure complex CHDs. Due to the complexity of the operation, extracorporeal circulation and a long time period are required for anesthesia, postoperative close monitoring in the intensive care unit (ICU), and assisted supportive treatment of cardiopulmonary function to survive the most dangerous postoperative stage. The relatively closed ICU environment, long period of separation, lack of knowledge of the disease, and other factors make the psychological pressure on parents far greater than on parents of children with other diseases[4-6]. The unhealthy psychological problems of the parents of these children not only affect the rehabilitation of children, but can also cause conflict between the doctor and patient, and tension between the doctor and the parents[7]. In this study, the parents of children with complicated CHD who underwent surgery were surveyed to understand their psychological needs, analyze influencing factors, identify major sources of stress, and explore intervention strategies to improve the medical care service model, nursing quality and satisfaction, and patient care.

MATERIALS AND METHODS
Building the survey
This study obtained authorization from Xia and Yan[8], the original author of the modified Chinese version of the Parental Needs Inventory for Critically Ill Children (M-CCFNI) and consulted the relevant national and international literature on the needs of parents of critically ill children. The current psychological needs of the parents of children with heart disease were evaluated. The basic information (general demographic and social data) of the parents included the parents’ gender, age, relationship to the child, cultural level, occupation, monthly family income, family residence, and other related data. The M-CCFNI scale has five dimensions and a total of 37 items which include the support of medical staff (Support Scale), parents’ own comfort (Comfort Scale), access to information (Information Scale), the need to be close to the children (Proximity Scale), and the Assurance Scale. The scale uses the Likert 4-point system for scoring. This study investigated the parents of children with CHD who had undergone surgery within 72 h after admission to the pediatric ICU (PICU).
### Table 1 General information on parents of the children

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<th>Measurement index</th>
<th>Variable</th>
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</tr>
<tr>
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<tr>
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<td>Junior high school and below</td>
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</tr>
<tr>
<td></td>
<td>3000-5999</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>&gt; 6000-10000</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>More than 10000</td>
<td>48</td>
</tr>
<tr>
<td>Home</td>
<td>City</td>
<td>69</td>
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<tr>
<td></td>
<td>Rural area</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Town</td>
<td>44</td>
</tr>
<tr>
<td>The only child</td>
<td>Yes</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>117</td>
</tr>
<tr>
<td>Religious beliefs</td>
<td>Yes</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>117</td>
</tr>
</tbody>
</table>

### Table 2 Scores of items in the M-CCFNI scale

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Item content</th>
<th>Score (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical staff support</td>
<td>1 Hope that before I enter the ICU for the first time, the medical staff can introduce me to the ICU</td>
<td>3.62 ± 0.58</td>
</tr>
<tr>
<td></td>
<td>4 Hope to be guided by medical staff when visiting the ICU</td>
<td>3.63 ± 0.52</td>
</tr>
<tr>
<td></td>
<td>6 Hope that medical staff will take the initiative to inform parents of the child’s condition and current situation</td>
<td>3.76 ± 0.46</td>
</tr>
<tr>
<td></td>
<td>12 When the condition changes, someone can call the parents in time</td>
<td>3.82 ± 0.39</td>
</tr>
<tr>
<td></td>
<td>15 Hope to know other experts who can solve children’s problems</td>
<td>3.53 ± 0.66</td>
</tr>
<tr>
<td>Number</td>
<td>Description</td>
<td>Score</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>23</td>
<td>Hope to provide spiritual and psychological support</td>
<td>3.61 ± 0.58</td>
</tr>
<tr>
<td>24</td>
<td>Hope that medical staff treat patients as relatives and sincerely care and take care of patients</td>
<td>3.78 ± 0.44</td>
</tr>
<tr>
<td>28</td>
<td>I hope to talk to the ICU medical staff about my bad emotions, such as guilt, anger, etc.</td>
<td>2.97 ± 1.02</td>
</tr>
<tr>
<td>29</td>
<td>Hope that medical staff will help like friends</td>
<td>3.54 ± 0.67</td>
</tr>
<tr>
<td>30</td>
<td>Hope that medical staff can patiently explain, comfort and psychologically counsel</td>
<td>3.59 ± 0.63</td>
</tr>
<tr>
<td>36</td>
<td>Sometimes family members are emotionally upset for the patient, and I hope the medical staff can understand</td>
<td>3.53 ± 0.63</td>
</tr>
<tr>
<td>8</td>
<td>Hope that family members have comfortable rest facilities in the waiting room</td>
<td>3.12 ± 0.89</td>
</tr>
<tr>
<td>13</td>
<td>Hope that there is a special waiting room for parents outside the ICU</td>
<td>3.00 ± 1.05</td>
</tr>
<tr>
<td>19</td>
<td>Hope that there will be a special waiting room for family members outside the ICU</td>
<td>3.48 ± 0.71</td>
</tr>
<tr>
<td>26</td>
<td>Hope that the hospital has humanized management and handles the relationship between doctors and patients’ family members</td>
<td>3.67 ± 0.51</td>
</tr>
<tr>
<td>3</td>
<td>Can understand the general information of the patient's doctor in charge and responsible nurse, such as job title, experience, level, etc.</td>
<td>3.52 ± 0.67</td>
</tr>
<tr>
<td>9</td>
<td>I hope to communicate with the same nurse every day to understand the patient’s condition</td>
<td>3.63 ± 0.54</td>
</tr>
<tr>
<td>14</td>
<td>Needs for understanding disease-related knowledge</td>
<td>3.56 ± 0.63</td>
</tr>
<tr>
<td>16</td>
<td>Know what kind of information needs to be asked of staff</td>
<td>3.59 ± 0.62</td>
</tr>
<tr>
<td>17</td>
<td>When you cannot go to the hospital to visit, you can call the responsible nurse or doctor to ask about the child’s condition</td>
<td>3.75 ± 0.46</td>
</tr>
<tr>
<td>22</td>
<td>Know every treatment the child is currently receiving</td>
<td>3.78 ± 0.45</td>
</tr>
<tr>
<td>25</td>
<td>Medical staff do not avoid the condition of the disease, and can talk to me about the possibility that the child's treatment effect is not significant</td>
<td>3.75 ± 0.46</td>
</tr>
<tr>
<td>27</td>
<td>Be informed when planning to change the treatment plan</td>
<td>3.76 ± 0.49</td>
</tr>
<tr>
<td>34</td>
<td>Know the purpose of a certain treatment for the patient</td>
<td>3.75 ± 0.48</td>
</tr>
<tr>
<td>35</td>
<td>I hope to receive dietary guidance and activity guidance for children with various diseases</td>
<td>3.72 ± 0.49</td>
</tr>
<tr>
<td>18</td>
<td>When parents have special circumstances, they hope to adjust the visiting time flexibly</td>
<td>3.57 ± 0.60</td>
</tr>
<tr>
<td>32</td>
<td>Hope to be able to accommodate and increase visitation opportunities in special circumstances</td>
<td>3.65 ± 0.58</td>
</tr>
<tr>
<td>33</td>
<td>Get information about the patient's condition every day</td>
<td>3.76 ± 0.47</td>
</tr>
<tr>
<td>37</td>
<td>I hope the doctor can make an appointment to explain the child’s condition</td>
<td>3.70 ± 0.62</td>
</tr>
<tr>
<td>2</td>
<td>Hope that the medical staff can explain the condition easily and understandably</td>
<td>3.69 ± 0.52</td>
</tr>
<tr>
<td>5</td>
<td>The medical staff can answer my questions truthfully</td>
<td>3.75 ± 0.45</td>
</tr>
<tr>
<td>10</td>
<td>Feel the care of medical staff for patients</td>
<td>3.69 ± 0.49</td>
</tr>
<tr>
<td>11</td>
<td>Let me understand the prognosis of the child</td>
<td>3.81 ± 0.40</td>
</tr>
<tr>
<td>20</td>
<td>Hope that medical staff will do their best and be responsible</td>
<td>3.82 ± 0.42</td>
</tr>
<tr>
<td>21</td>
<td>Can feel the condition is expected to improve</td>
<td>3.80 ± 0.41</td>
</tr>
<tr>
<td>31</td>
<td>Can know the specific circumstances of the change</td>
<td>3.75 ± 0.47</td>
</tr>
</tbody>
</table>

ICU: Intensive care unit.

Methods of investigation

This survey involved completing a questionnaire online. First, the researcher adopted the domestic mature electronic questionnaire system design to form the electronic version of the questionnaire, and used repeated tests to ensure that the content of the electronic version of the questionnaire was completely consistent with the paper questionnaire. Then, the research team used the WeChat electronic version of the questionnaire to create a QR code for the questionnaire, and the survey participants used the mobile terminal to scan the code to complete the questionnaire. Each terminal was restricted to completing the questionnaire only once. This questionnaire survey adopted an anonymous method, and the parents were able to truly express their opinions without being affected by other factors.
Table 3 M-CCFNI scores of various dimensions and total score of parents of children with complicated congenital heart disease

<table>
<thead>
<tr>
<th>Demand dimension</th>
<th>Score (mean ± SD)</th>
<th>Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition assurance</td>
<td>3.76 ± 0.46</td>
<td>1</td>
</tr>
<tr>
<td>Get information</td>
<td>3.66 ± 0.56</td>
<td>2</td>
</tr>
<tr>
<td>The need to be close to the child</td>
<td>3.65 ± 0.57</td>
<td>3</td>
</tr>
<tr>
<td>Support from medical staff</td>
<td>3.58 ± 0.65</td>
<td>4</td>
</tr>
<tr>
<td>Parents’ own comfort</td>
<td>3.31 ± 0.86</td>
<td>5</td>
</tr>
<tr>
<td>Total score</td>
<td>3.62 ± 0.62</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 Scores of top 5 needs of parents of children with complicated congenital heart disease

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Entry</th>
<th>Score (mean ± SD)</th>
<th>&quot;Very important&quot; proportion/%</th>
<th>Sort</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>Hope that medical staff will do their best and be responsible</td>
<td>3.82 ± 0.42</td>
<td>83.3</td>
<td>1</td>
</tr>
<tr>
<td>SS</td>
<td>When the condition changes, someone can call the parents in time</td>
<td>3.82 ± 0.39</td>
<td>81.9</td>
<td>2</td>
</tr>
<tr>
<td>AS</td>
<td>Allow me to understand the prognosis of the child</td>
<td>3.81 ± 0.40</td>
<td>81.9</td>
<td>3</td>
</tr>
<tr>
<td>AS</td>
<td>Can feel the condition is expected to get better</td>
<td>3.80 ± 0.41</td>
<td>80.9</td>
<td>4</td>
</tr>
<tr>
<td>IS</td>
<td>Know every treatment the child is currently receiving</td>
<td>3.78 ± 0.45</td>
<td>76.5</td>
<td>5</td>
</tr>
</tbody>
</table>

AS: Assurance scale; SS: Support scale; IS: Information scale.

RESULTS

General information on parents of the children with complicated CHD is shown in Table 1. The needs of parents of children with complicated CHD are shown in Tables 2-4. Influencing factors on the needs of parents of children with complicated CHD are shown in Table 5.

DISCUSSION

The results of this study showed that the needs of parents of children with complex CHD after surgery are multifaceted, with a higher degree of demand as shown in Tables 3 and 4, with an average score of (3.62 ± 0.62). In this study, single factor analysis of the needs of parents of children with CHD is shown in Table 5. It was found that age, educational level, and place of residence of the parents were correlated with the five dimensions of the needs of parents of these children. Therefore, more attention should be paid to the parents of children with complicated CHD who are admitted to the ICU and try to meet their needs.

This study showed that condition assurance is the most important requirement for parents of children with complicated CHD after surgery, which is consistent with the findings in other studies[9,10]. And three of the first five needs of parents are disease assurance needs. In this study, the score of "Hope that medical staff will do their best and be responsible" was the highest (3.82 ± 0.42), and 83.3% of the parents thought that this demand was very important. Within 72 h after admission to ICU, the patient's condition is still in an unstable state. Parents are most concerned about whether the child can be treated effectively to ensure that the child can pass through the critical period safely. It is suggested that medical staff should focus on meeting the disease guarantee needs of children’s parents, including ensuring that children get the best treatment, and truthfully answer parents' questions, so that they can tell them about the progress of the disease. In the actual clinical work, when the child is sick, the family can only rely on the treatment and care of the medical staff, and often have high expectations for the treatment and prognosis of the child. When the treatment outcome of the child is not satisfactory, it is difficult for the family to understand and accept it. It is very easy to produce doctor-patient conflicts. Therefore, ICU medical staff should not only make the family members of patients feel the hope of...
<table>
<thead>
<tr>
<th>Influencing factors</th>
<th>Dimension 1: Medical staff support</th>
<th>Dimension 2: Parents’ own comfort</th>
<th>Dimension 3: Getting information</th>
<th>Dimension 4: Close to the needs of children</th>
<th>Dimension 5: Condition assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Demand score</td>
<td>F value</td>
<td>P value</td>
<td>Demand score</td>
<td>F value</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.635</td>
<td>0.202</td>
<td></td>
<td>9.320</td>
<td>0.003*</td>
</tr>
<tr>
<td>≤ 35</td>
<td>22.40 ± 2.22</td>
<td></td>
<td></td>
<td>25.60 ± 3.78</td>
<td></td>
</tr>
<tr>
<td>&gt; 35</td>
<td>21.94 ± 2.21</td>
<td></td>
<td></td>
<td>25.87 ± 2.54</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.637</td>
<td>0.426</td>
<td></td>
<td>1.304</td>
<td>0.255</td>
</tr>
<tr>
<td>Male</td>
<td>22.10 ± 2.08</td>
<td></td>
<td></td>
<td>26.19 ± 2.68</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22.37 ± 2.28</td>
<td></td>
<td></td>
<td>26.62 ± 2.32</td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>1.307</td>
<td>0.254</td>
<td></td>
<td>1.694</td>
<td>0.195</td>
</tr>
<tr>
<td>Father</td>
<td>22.02 ± 2.06</td>
<td></td>
<td></td>
<td>26.17 ± 2.67</td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>22.40 ± 2.28</td>
<td></td>
<td></td>
<td>26.63 ± 2.33</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>2.532</td>
<td>0.113</td>
<td></td>
<td>2.359</td>
<td>0.126</td>
</tr>
<tr>
<td>Below college</td>
<td>22.04 ± 2.46</td>
<td></td>
<td></td>
<td>26.04 ± 2.78</td>
<td></td>
</tr>
<tr>
<td>College degree and above</td>
<td>22.54 ± 1.91</td>
<td></td>
<td></td>
<td>26.96 ± 1.93</td>
<td></td>
</tr>
<tr>
<td>Monthly income</td>
<td>1.704</td>
<td>0.193</td>
<td></td>
<td>1.443</td>
<td>0.231</td>
</tr>
<tr>
<td>≤ 6000 yuan</td>
<td>22.10 ± 2.39</td>
<td></td>
<td></td>
<td>26.23 ± 2.62</td>
<td></td>
</tr>
<tr>
<td>&gt; 6000 yuan</td>
<td>22.52 ± 1.95</td>
<td></td>
<td></td>
<td>26.84 ± 2.14</td>
<td></td>
</tr>
<tr>
<td>Place of residence</td>
<td>5.213</td>
<td>0.023*</td>
<td></td>
<td>5.151</td>
<td>0.022</td>
</tr>
<tr>
<td>Rural area</td>
<td>22.02 ± 2.29</td>
<td></td>
<td></td>
<td>26.21 ± 2.59</td>
<td></td>
</tr>
<tr>
<td>City</td>
<td>22.77 ± 2.01</td>
<td></td>
<td></td>
<td>27.00 ± 2.04</td>
<td></td>
</tr>
<tr>
<td>Only child</td>
<td>0.075</td>
<td>0.785</td>
<td></td>
<td>2.557</td>
<td>0.111</td>
</tr>
<tr>
<td>No</td>
<td>22.32 ± 2.10</td>
<td></td>
<td></td>
<td>26.55 ± 2.28</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22.23 ± 2.39</td>
<td></td>
<td></td>
<td>26.40 ± 2.66</td>
<td></td>
</tr>
<tr>
<td>Religious belief</td>
<td>0.711</td>
<td>0.400</td>
<td></td>
<td>0.054</td>
<td>0.816</td>
</tr>
<tr>
<td>No</td>
<td>22.33 ± 2.23</td>
<td></td>
<td></td>
<td>26.49 ± 2.45</td>
<td></td>
</tr>
</tbody>
</table>
improvement of the patient's condition, but also let the family members correctly understand the prognosis of the patients, and form a correct and reasonable psychological expectation of the prognosis of the patients, so as to reduce the conflict between doctors and patients.

In addition, the demand for information was also relatively high. Nurses must provide parents with information about the child, such as the child’s recovery from the disease, medication use, and mental state while the child’s condition is stable. In this study, the need to get close to the child was slightly lower than the need to obtain information. In a study of the needs of parents of newborns in the ICU by Thomi et al.[11], “being with the child” was the most important need. The children and their parents are prone to developing unhealthy emotions such as separation anxiety, which is not conducive to the children’s early rehabilitation and nurse-patient communication. Therefore, when the child or the parent has special circumstances, the nursing staff should adjust the visiting time and frequency in a timely manner. It is also important to keep in touch with the parents of the child in a variety of ways, so that they can understand the changes in the child’s condition dynamically and in real time, meet the psychological needs for the child’s closeness, and relieve nervousness. At the same time, the establishment of a semi-closed or fully open PICU management model or family participatory nursing model can be explored.

This study found that parents of children with complex CHD place too much emphasis on the treatment of children, and they neglect to pay attention to themselves. Gramszlo et al.[12] believe that the concept of centering on the parents should be integrated into the ICU’s child-centered medical care service model. In 2019, Golfenshtein et al.[13] showed that if the needs of parents of ICU children can be effectively met, this can reduce their anxiety, provide a good social support system for children, and promote their recovery. This also suggests that nursing staff should pay attention to providing psychological support services to parents of children during the nursing process.

CONCLUSION

With the continuous renewal of nursing concepts, the importance of child- and parent-centered concepts and family support therapy in the treatment process has been increasingly recognized by hospital administrators and clinical nursing staff. In the treatment and nursing process of children who undergo complicated surgery for CHD, nursing staff should also pay attention to the mood changes of the caregivers, relieve and guide their emotions, and help them establish the correct attitude and confidence to overcome the disease which can reduce the burden of caregivers in a variety of ways[14], in order to provide more and better positive support to children and promote their recovery. On the other hand, satisfying the reasonable psychological needs of the parents of these children can improve satisfaction and help build a harmonious nurse-patient relationship.
ARTICLE HIGHLIGHTS

Research background
Parents of children with complicated congenital heart disease (CHD) have different needs after surgery. Little literature reports the impact factors for psychological needs of patents of children with complicated CHD.

Research motivation
To investigate the status quo of the needs of parents of children after surgery for complex CHD, and analyze the influencing factors, in order to provide a theoretical basis for formulating corresponding nursing countermeasures.

Research objectives
To provide a theoretical basis for formulating corresponding nursing countermeasures.

Research methods
A modified Chinese version of the Critical Care Family Needs Inventory (M-CCFNI) was used to select 200 parents of children with complex CHD after surgery within 72 h after admission to intensive care unit (ICU) in our hospital to conduct an online questionnaire survey. The aim was to understand the needs of parents in relation to the following five aspects: The support from medical staff, comfort of the parents themselves, the acquisition of information, their closeness to the children, and assurance of the child’s condition.

Research results
Parents of children with complex CHD had a higher degree of demand, especially in terms of condition assurance, acquisition of information, and closeness to the children. The age, education level, and residence of the parents were related to the five dimensions of the needs of parents of children with complex CHD who had undergone surgery.

Research conclusions
In practice, nurses should formulate corresponding nursing strategies based on the different cultural and social backgrounds of parents after complex CHD surgery to meet their different needs, and improve satisfaction. These findings provide a theoretical basis for constructing a family participatory nursing model for children in the intensive care unit in the future.

Research perspectives
How to provide psychological intervention for parents of children admitted to ICU after complex CHD should be further explored in the future.

FOOTOTES

Author contributions: Zhu JH, Jin CD and Tang XM designed the research study; Jin CD performed the research; Zhu JH and Tang XM analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Medical Ethics Committee of Children's Hospital Affiliated to Zhejiang University School of Medicine.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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Zhu JH et al. Psychological needs of CHD children’s parents

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S-Editor: Gao CC
L-Editor: Wang TQ
P-Editor: Gao CC

REFERENCES

Quantitative differentiation of malignant and benign thyroid nodules with multi-parameter diffusion-weighted imaging

Xiang Zhu, Jia Wang, Yan-Chun Wang, Ze-Feng Zhu, Jian Tang, Xiao-Wei Wen, Ying Fang, Jun Han

BACKGROUND
The value of conventional magnetic resonance imaging in the differential diagnosis of thyroid nodules is limited; however, the value of multi-parameter diffusion-weighted imaging (DWI) in the quantitative evaluation of thyroid nodules has not been well determined.

AIM
To determine the utility of multi-parametric DWI including mono-exponential, bi-exponential, stretched exponential, and kurtosis models for the differentiation of thyroid lesions.

METHODS
Seventy-nine patients (62 with benign and 17 with malignant nodules) underwent multi-b value diffusion-weighted imaging of the thyroid. Multiple DWI parameters were obtained for statistical analysis.

RESULTS
Good agreement was found for diffusion parameters of thyroid nodules. Malignant lesions displayed lower diffusion parameters including apparent diffusion coefficient (ADC), the true diffusion coefficient (D), the perfusion fraction (f), the distributed diffusion coefficient (DDC), the intravoxel water diffusion heterogeneity (α) and kurtosis model-derived ADC (Dapp), and higher apparent diffusional kurtosis (Kapp) than benign entities (all \( P < 0.01 \)), except for...
the pseudodiffusion coefficient (D*) (P > 0.05). The area under the ROC curve (AUC) of the ADC (0 to 1000) was not significantly different from that of the ADC (0 to 2000) ADC (0 to 1000), D, DDC, Dapp and Kapp (all P > 0.05), but was significantly higher than the AUC of D*, f and α (all P < 0.05) for differentiating benign from malignant lesions.

CONCLUSION
Multiple DWI parameters including ADC, D, f, DDC, α, Dapp and Kapp could discriminate benign and malignant thyroid nodules. The metrics including D, DDC, Dapp and Kapp provide additional information with similar diagnostic performance of ADC, combination of these metrics may contribute to differentiate benign and malignant thyroid nodules. The ADC calculated with higher b values may not lead to improved diagnostic performance.

Key Words: Thyroid nodule; Magnetic resonance imaging; Diffusion-weighted imaging; Quantitative study; Sensitivity; Specificity

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Core Tip: Multiple diffusion coefficient parameters obtained by fitting with mono-exponential, biexponential, stretched exponential, and kurtosis diffusion-weighted imaging models are feasible techniques for investigating thyroid nodules; The metrics including D, distributed diffusion coefficient, Dapp and Kapp provide additional information with similar diagnostic performance of ADC, and combination of these metrics may contribute to differentiate benign and malignant thyroid nodules; The apparent diffusion coefficient calculated with a mono-exponential model using a single pair of conventional b values (b = 1000 s/mm²) have similar diagnostic performance to those calculated with higher b values (b value > 1000 s/mm²).

URL: https://www.wjgnet.com/2307-8960/full/v10/i24/8587.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i24.8587

INTRODUCTION
Thyroid nodules are common lesions that occur thyroid cells growth into an abnormal lump within the thyroid gland; these nodules are often palpable and radiologically distinct from the surrounding parenchyma[1,2]. As with most common endocrine tumors, thyroid nodules have a reported prevalence of 4%-7% in the adult population on physical examination (identified by palpation), and 10 times more nodules are identified with imaging studies[1]. Approximately 5% of detected thyroid nodules are diagnosed as malignancies[3]. The incidence of thyroid cancer has continuously and sharply increased worldwide at a rate higher than any other cancer and has tripled over the past three decades[4-6].

The treatment options recommended for benign and malignant thyroid lesions are completely different; surgical treatment is recommended for the vast majority of thyroid cancer, while most benign nodules can be safely followed with an active surveillance management approach[2]. Therefore, initial management recommendations are very dependent on preoperative studies designed to distinguish between malignant and benign thyroid nodules[1,2,7]. Ultrasonography (US) has been used as the first-line imaging modality for patients with known or suspected thyroid cancer[6]. US also provides guidance for fine-needle aspiration biopsy (FNAB). However, evaluation by US is operator-dependent, and no single sonographic feature is of sufficient diagnostic value to accurately differentiate malignant nodules from benign nodules[9]. Although FNAB is the most accurate tool for evaluating thyroid nodules, it is an invasive procedure associated with possible complications, and its accuracy may vary depending on many factors, such as the skills of the operator and the location of aspiration[7,9].

Currently, diffusion-weighted imaging (DWI) is becoming a very useful tool for the detection and characterization of head and neck cancer. Restricted and hindered diffusion of water molecules within malignant tumors lead to high contrast on diffusion-weighted (DW) images compared with images of normal tissues thus facilitating the diagnosis. The acquired DW images are often postprocessed using standard mono-exponential fitting, which applies a linear shape to obtain apparent diffusion coefficient (ADC) maps. More restricted diffusion is observed in malignant tumors than in benign lesions, which is indicated by a reduction in the ADC[10]. Previous studies of thyroid cancer have indicated that ADC...
parameters can distinguish malignant and benign thyroid nodules. In routine practice, however, the b values applied in thyroid DWI studies are usually lower than 1000 s/mm². Moreover, the diagnostic performance of the ADC calculated with higher b values (b value > 1000 s/mm²) has not been well investigated in patients with thyroid cancer.

The microscopic motion of water molecules detected by DWI is influenced by diffusion of water molecules and by microcirculation of blood in capillary networks[10]. A specialized bi-exponential model known as intravoxel incoherent motion (IVIM) can separate the incoherent motion of water molecules in the randomly oriented capillaries from molecular diffusion in the extravascular space[10, 11]. In addition, these two components can be quantitatively expressed by three parameters: The true diffusion coefficient (D), the pseudodiffusion coefficient (D*), and the perfusion fraction (f)[10,11]. Recently, only one study used IVIM to evaluate thyroid cancer and reported that IVIM data might be helpful for differentiating malignant thyroid nodules from benign nodules[10].

Different from the bi-exponential model, the stretched exponential DWI model has been recently proposed by Bennett et al[12] and provides a measure of signal deviation from the mono-exponential behavior caused by pseudoperfusion effects; thus, this model provides information on tissue heterogeneity and diffusion simultaneously with two parameters: the distributed diffusion coefficient (DDC) and the intravoxel water diffusion heterogeneity (n)11[13,14]. In addition, diffusion kurtosis models yield an estimate of the excess kurtosis of the diffusion displacement probability distribution with two parameters, Dapp and Kapp, which are produced from the DKI model and represent the diffusion coefficient and the diffusional kurtosis, respectively. To the best of our knowledge, this is the first study to evaluate thyroid nodules with ADCs calculated with higher b values (b value > 1000 s/mm²) and to compare the diagnostic performance of diffusion parameters fitted by mono-exponential, bi-exponential, stretched exponential, and kurtosis DWI models to quantitatively differentiate thyroid cancer.

The aim of this study was to prospectively evaluate the following: (1) To determine whether ADCs calculated with higher b values (b value > 1000 s/mm²) had benefits over ADCs calculated with conventional b values (b = 1000 s/mm²) to quantitatively differentiate thyroid cancer; and (2) to evaluate the feasibility and diagnostic performance of using multiple diffusion coefficient parameters by fitting with mono-exponential (ADCs fitted with conventional and higher b values), bi-exponential (D, D* and f), stretched exponential (DDC and n), and kurtosis DWI (Dapp and Kapp) models to quantitatively differentiate thyroid cancer.

MATERIALS AND METHODS

Patients

This study was approved by the First Hospital of Jiaxing Research and Ethics Committee. Written informed consent was obtained from all participants, and the hard copy was archived in the Department of Radiology at the First Hospital of Jiaxing. From January 2017 to July 2019, 79 consecutive patients with thyroid nodules determined by US who were scheduled to undergo thyroidectomy were prospectively enrolled. Multiparameter magnetic resonance imaging (MRI) examinations (including multiple b value DWI) were performed for each patient. The mean age of the included patients was 53 years (range, 20-72 years). Fifty-four of the 78 patients were female. All the patients enrolled in this study had been scheduled to undergo thyroidectomy within 2 wk. Histopathology revealed that 62 patients had benign nodules, including nodular goiter (n = 48) and thyroid adenoma (n = 14), while 17 patients had malignant nodules, including papillary thyroid carcinoma (n = 12), medullary thyroid carcinoma (n = 4), and follicular thyroid carcinoma (n = 1).

Image acquisition

All MRI examinations were performed in the prone position using a 3.0 Tesla (T) MRI scanner (Discovery MR750; GE Healthcare, United States) with an eight-channel neurovascular phased-array coil. Patients were instructed to breathe calmly and avoid swallowing as much as possible and practice this. The MRI examination consisted of conventional multiplanar (sagittal, axial, and coronal planar) T1- and T2-weighted imaging scans followed by multiple b value DWI scans. The duration of the whole examination was approximately 30 min. Multiple b value DWI was performed by using a standard, bipolar, single-shot echo-planar sequences in the axial plane. The DWI images were obtained with a repetition time/echo time (TR/TE) of 3000 ms/79.3 ms, section thickness of 4 mm, gap of 1.5 mm, field of view of 200 mm × 200 mm, and matrix of 128 mm× 128 mm. Parallel imaging was used with an acceleration factor of 2. A local shim box covering the thyroid was applied to minimize susceptibility artifacts. Thirteen b values from 0 to 2000 s/mm² (0, 30, 50, 80, 100, 150, 200, 400, 600, 800, 1000, 1500, and 2000 s/mm²) were used in three orthogonal diffusion directions. The acquisition time for multiple b value DWI sequences was 1 min 57 s.

DWI images were transferred to a PC and postprocessed with mono-exponential, bi-exponential, stretched exponential, and kurtosis models using in-house software written in Matlab (version R2014b; MathWorks, Natick, MA, United States). Parameter maps were generated and included the mean ADC,
D, D*, f, DDC, α, kurtosis model-derived ADC (Dapp), and apparent diffusional kurtosis (Kapp) values. Two independent thyroid radiologists (J.W. and X.Z. with 15 and 18 years of head and neck MR diagnostic experience, respectively) who were blinded to the histopathological results performed the postprocessing. The regions of interest were as large as possible to encompass the whole solid portion of the thyroid nodule while carefully avoiding areas of obvious necrosis, cystic degeneration, hemorrhagic, or calcified portions, according to T1-, T2-, and contrast-enhanced T1-weighted images for reference. The corresponding mathematical expressions are as follows.

**Mono-exponential:** ADC was automatically calculated by using the mono-exponential model with b values: $S(b) = S_0 \cdot \exp (-b \cdot ADC)$ where $S(b)$ is the diffusion sensitizing factor; $S_0$ is the signal intensity without a diffusion gradient; and $S(b)$ is the signal intensity at a particular b value. In our study, ADC$	extsubscript{(0 to 1000)}$ was calculated with b values of 0 s/mm$^2$ and 1000 s/mm$^2$, ADC$	extsubscript{(0 to 1000)}$ was calculated with b values from 0 s/mm$^2$ to 1000 s/mm$^2$, and ADC$	extsubscript{(0 to 2000)}$ was calculated with b values of 0 s/mm$^2$ and 2000 s/mm$^2$. ADC$	extsubscript{(0 to 1000)}$ was calculated with b values from 0 s/mm$^2$ to 2000 s/mm$^2$.

**Bi-exponential:** According to the bi-exponential model, the mathematical relationship between b values and signal intensities was described using the following formula: $S(b) = S_0 \cdot \left(1 \cdot f \cdot \exp (-b \cdot D) + f \cdot \exp (-b \cdot D^*)\right)$ where $S(b)$ is the signal intensity at a particular b value; $D$ is the true diffusion coefficient that reflects random motion of intra- and intercellular water molecules (slow component of diffusion); $D^*$ is the diffusion parameter representing incoherent microcirculation within the voxel (perfusion related diffusion, or fast component of diffusion); and $f$ is the fraction of the diffusion ($0 \leq f \leq 1$) linked to microcirculation.

**Stretched exponential:** By fitting the stretched exponential model, DDC and $\alpha$ were calculated as follows: $S(b) = S_0 \cdot \left[1 \cdot f \cdot \exp (-b \cdot D) + f \cdot \exp (-b \cdot D^*)\right]$ where $S(b)$ is the signal intensity at a particular b value; $D^*$ is the kurtosis model-derived ADC (in mm$^2$/s); and $\alpha$ represents the anomalous exponent term that parameterizes “tissue heterogeneity” ($0 \leq \alpha \leq 1$).

**Kurtosis-exponential:** The multi-b value DWI images fitted the following diffusion kurtosis imaging (DKI) signal decay equation:

$$S(b) = S_0 \cdot \exp (-b \cdot D_{\text{app}} + 1/6 \cdot b^2 D_{\text{app}}^2 K_{\text{app}})$$

where $S(b)$ is the signal intensity at a particular b value; $D_{\text{app}}$ is the kurtosis model-derived ADC (in mm$^2$/s); and $K_{\text{app}}$ is the apparent diffusional kurtosis (dimensionless parameter), which suggest that the status of water molecular motion deviates from a Gaussian distribution. A minimum Kapp value showed that the curve fit closely to a Gaussian distribution. However, increased Kapp indicated increased contributions of the lesion area attributable to kurtosis behavior.

**Histopathological examination**

Histopathological examination findings from surgical specimens obtained after radical thyroidectomy or lobectomy were obtained from pathology reports, which were reviewed by two pathologists (X.W.W. and Y.F. with 25 and 18 years of experience with pathological diagnosis, respectively) specializing in the pathological diagnosis of thyroid diseases. According to the characteristics of the thyroid nodules, patients were divided into two groups. The benign tumor group included those with nodular goiter and thyroid adenoma. The malignant tumor group included those with papillary thyroid carcinoma, medullary thyroid carcinoma, and follicular thyroid carcinoma. Histological subtype was determined for all lesions by immunohistochemical analysis.

**Statistical analysis**

Data are presented as the mean ± standard deviation (SD). All statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL, United States). The Mann-Whitney U test was used to compare the diffusion parametric differences in the subgroups. A $P$ value < 0.05 was deemed statistically significant. Intrarater reliability between the two radiologists was assessed by using the intraclass correlation coefficient (ICC). According to Fleiss[15], an ICC of 0.4 represents poor agreement, a value of 0.75 represents good agreement, and a value between 0.4 and 0.75 represents fair to moderate agreement.

Moreover, receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic performance of diffusion parameters for detecting malignant tumors. Sensitivity and specificity were computed at the optimal cutoff value for each diffusion parameter that maximized the Youden index. The area under the ROC curve (AUC) was compared between the ADC and other diffusion parameters by using Z test.

**RESULTS**

T2-weighted images, ADC maps, D map, D* map, f map, DDC map, α map, Dapp map, Kapp map, and histopathological maps of representative cases of the benign and malignant patient groups are shown in

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*Zhu X et al. Quantitative differentiation of malignant and benign thyroid nodules*
Table 1 Interreader reproducibility of measurement of diffusion parameters of thyroid nodules

<table>
<thead>
<tr>
<th>Diffusion parameter</th>
<th>ICC</th>
<th>95%CI</th>
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<tbody>
<tr>
<td>MonoeXponential</td>
<td></td>
<td></td>
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<tr>
<td>ADC_{[0 \text{ and } 1000]}</td>
<td>0.944</td>
<td>(0.852, 0.979)</td>
</tr>
<tr>
<td>ADC_{[0 \text{ to } 1000]}</td>
<td>0.938</td>
<td>(0.898, 0.962)</td>
</tr>
<tr>
<td>ADC_{[0 \text{ and } 2000]}</td>
<td>0.904</td>
<td>(0.844, 0.941)</td>
</tr>
<tr>
<td>ADC_{[0 \text{ to } 2000]}</td>
<td>0.942</td>
<td>(0.905, 0.962)</td>
</tr>
<tr>
<td>Biexponential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0.949</td>
<td>(0.921, 0.967)</td>
</tr>
<tr>
<td>D*</td>
<td>0.935</td>
<td>(0.900, 0.958)</td>
</tr>
<tr>
<td>f</td>
<td>0.897</td>
<td>(0.844, 0.933)</td>
</tr>
<tr>
<td>stretched exponential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDC</td>
<td>0.994</td>
<td>(0.990, 0.996)</td>
</tr>
<tr>
<td>α</td>
<td>0.973</td>
<td>(0.958, 0.983)</td>
</tr>
<tr>
<td>Kurtosis DWI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapp</td>
<td>0.787</td>
<td>(0.685, 0.859)</td>
</tr>
<tr>
<td>Kapp</td>
<td>0.855</td>
<td>(0.782, 0.905)</td>
</tr>
</tbody>
</table>

ADC: Apparent diffusion coefficient; DWI: Diffusion-weighted imaging; D: Slow diffusion coefficient; D*: Fast diffusion coefficient; f: Fraction of fast diffusion; DDC: Distributed diffusion coefficient; ICC: Intraclass correlation; α: Anomalous exponent term; Dapp: Mean diffusivity; Kapp: Mean kurtosis.

Figures 1 and 2. In addition, the plot of the decay in diffusion-weighted signal intensity fitted by mono-exponential, bi-exponential, stretched-exponential, and kurtosis models, and fitted by a mono-exponential model with different b values for the benign and malignant thyroid nodules are shown in Figures 1 and 2.

The interobserver reproducibility between the two radiologists for determining thyroid nodule diffusion parameter measurements was calculated by using the ICC (Table 1). Good agreement was found for all metrics including ADC, D, D*, f, DDC, α, Dapp, and Kapp, indicating good reproducibility between the two readers. Therefore, the diffusion parameters measured by the first radiologist (Z.X.) were included for comparison. Table 2 shows the quantitative comparison of diffusion parameters between benign and malignant thyroid nodules. The diffusion parameters including ADC, D, f, DDC, α, and Dapp were significantly lower in malignant thyroid nodules than in benign nodules (all P < 0.01). Kapp was significantly higher in malignant thyroid nodules than in benign nodules (P < 0.01). D* was not significantly different between the two groups (P > 0.05).

The results of the ROC analyses of diffusion parameters for differentiating malignant nodules from benign nodules are summarized in Table 3. ROC curves of the ADC_{[0 \text{ and } 1000]}, ADC_{[0 \text{ and } 2000]}, ADC_{[0 \text{ to } 1000]}, ADC_{[0 \text{ to } 2000]}, D, D*, f, DDC, α, Dapp and Kapp are presented in Figure 3. ROC analysis demonstrated that ADC_{[0 \text{ and } 1000]} metrics showed trends toward higher AUC values than the ADC_{[0 \text{ and } 2000]}, ADC_{[0 \text{ to } 1000]}, and ADC_{[0 \text{ to } 2000]} using an ADC_{[0 \text{ to } 1000]} cutoff value of 1.5 × 10^3 mm^2/s, and malignant nodules could be diagnosed with a sensitivity of 72.6% and a specificity of 100%, but none of these differences reached statistical significance (all P > 0.05). The ADC_{[0 \text{ and } 1000]}, ADC_{[0 \text{ to } 2000]}, and Kapp metrics had significantly higher AUC values than D*, f, and α (all P < 0.05). The ADC_{[0 \text{ and } 2000]}, ADC_{[0 \text{ to } 2000]}, and D metrics had significantly higher AUC values than D*, f (all P < 0.05). The DDC, and Dapp metrics had significantly higher AUC values than D* (all P < 0.05).

DISCUSSION

To our best of knowledge, this work is the first study to investigate the feasibility of using multiple diffusion coefficient parameters by fitting with mono-exponential, bi-exponential, stretched exponential, and kurtosis DWI models to quantitatively differentiate malignant thyroid nodules from benign thyroid nodules. All parameters of the four models showed high interobserver agreement, suggesting that measurement of these parameters had good reproducibility and reliability.
Table 2 Comparison of diffusion parameters between benign and malignant thyroid nodules

<table>
<thead>
<tr>
<th>Diffusion parameter</th>
<th>Benign nodules</th>
<th>Malignant nodules</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mono-exponential</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC (0 and 1000)</td>
<td>1.85 ± 0.24</td>
<td>1.29 ± 0.27</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ADC (0 to 1000)</td>
<td>1.79 ± 0.021</td>
<td>1.19 ± 0.23</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ADC (0 and 2000)</td>
<td>1.35 ± 0.15</td>
<td>0.95 ± 0.15</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ADC (0 to 2000)</td>
<td>1.41 ± 0.15</td>
<td>0.95 ± 0.15</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Biexponential</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>1.34 ± 0.41</td>
<td>0.89 ± 0.26</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>D*</td>
<td>22.08 ± 18.53</td>
<td>26.09 ± 20.87</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>f</td>
<td>0.38 ± 0.19</td>
<td>0.30 ± 0.14</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Stretched exponential</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDC</td>
<td>2.15 ± 0.62</td>
<td>1.45 ± 0.51</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>a</td>
<td>0.78 ± 0.19</td>
<td>0.67 ± 0.19</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Kurtosis DWI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapp</td>
<td>2.88 ± 0.73</td>
<td>2.11 ± 0.67</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Kapp</td>
<td>0.57 ± 0.12</td>
<td>0.85 ± 0.19</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

ADC: Apparent diffusion coefficient; D: Slow diffusion coefficient; D*: Fast diffusion coefficient; f: Fraction of fast diffusion; DDC: Distributed diffusion coefficient; a: Anomalous exponent term; DWI: Diffusion-weighted imaging; Dapp: Mean diffusivity; Kapp, mean kurtosis. The ADC, D, D*, DDC, and Dapp are given in units of $10^{-3}$ mm$^2$/s. P values from statistical comparison between benign and malignant nodules were obtained by using the Mann-Whitney U test.

Previous studies on DWI in thyroid cancer have mostly focused on mono-exponential models with conventional b values (b value ≤ 1000 s/mm$^2$), and most studies have suggested that ADCs of malignant lesions were significantly lower than those of benign lesions[9,16-19]. Similarly, in our study, the ADC values (0 and 1000) and ADC values (0 and 2000) showed that malignant thyroid lesions had significantly lower ADCs than benign lesions, with AUC values of 0.879 and 0.882, respectively. Generally, although higher b values might produce more susceptibility to distortions and could increase the noise in DWI images, higher b values produced more diffusion weighting and therefore higher contrast between lesions and normal tissue[16]. Recent reports have shown advantages of using a higher b value (b value > 1000 s/mm$^2$) for DWI and ADC calculations for the diagnosis of acute stroke[20], malignant lymphoma[21], and prostate cancer[22]. In our study, although the ADC values (0 and 2000) and ADC values (0 to 2000) showed relatively higher sensitivities of 79.0% and 77.4%, respectively, than ADC values (0 and 1000) sensitivities of 64.5% and 72.6%, respectively, the ADC values (0 and 2000) and ADC values (0 to 2000) showed similar diagnostic performance to the ADC values (0 and 1000) and ADC values (0 to 2000). With AUC values of 0.874 and 0.878, respectively. Thus, our study indicates that DWI acquired with regular b values (b = 1000 s/mm$^2$) can be used to calculate DWI parameters similar to those obtained with DWI acquired with higher b values in patients with thyroid nodules. This phenomenon has also been reported by Eghtedari, M. on quantitative breast DWI for breast cancer[23]. Additionally, the ADC derived from a mono-exponential model with more than two b values is theoretically good for ADC fitting. In our study, the ADC values (0 to 2000) showed a relatively higher sensitivity of 72.6% than the that of the ADC values (0 and 1000) of 64.5%; the ADC values (0 to 2000) showed similar sensitivity of 77.4% to that of the ADC values (0 and 1000) of 79.0%. In addition, the diagnostic performance was similar between the ADC values (0 to 2000) and between the ADC values (0 and 2000) and ADC values (0 to 2000). Therefore, if the ADC fitted with the mono-exponential model alone was used to differentiate malignant thyroid nodules from benign thyroid nodules, using a single pair of b values (usually 0 s/mm$^2$ and 1000 s/mm$^2$) was acceptable for ADC calculation.

Bi-exponential IVIM DWI is a method initially proposed by Le Bihan et al[24] to quantitatively assess the microscopic motion that occurs at the subvoxel scale on MRI. D values mainly reflect the molecular diffusion of water protons. The D* value and f value mainly reflect perfusion status. In our study, the D values of malignant thyroid nodules were significantly lower than those of benign thyroid nodules. This finding was similar to the results of previous studies of thyroid cancer[10], breast cancer[11], nasopharyngeal carcinoma[25], prostate cancer[26], and metastatic lymph nodes in the head and neck[27]. This phenomenon might due to the rapid cellular proliferation, high cell density and reduced extracellular space in malignant thyroid lesions. In addition, the AUC of the D was slightly lower than that of the ADC value obtained from the mono-exponential model but was not significantly different.
### Table 3 Diagnostic performance of diffusion parameters for differentiating malignant thyroid nodules from benign thyroid nodules

<table>
<thead>
<tr>
<th>Diffusion parameter</th>
<th>AUC</th>
<th>Cut-off value</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Youden index</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mono-exponential</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ADC*(0 and 1000)</td>
<td>0.879</td>
<td>1.6</td>
<td>64.5</td>
<td>100.0</td>
<td>0.645</td>
<td>Ref.</td>
</tr>
<tr>
<td>ADC*(0 and 2000)</td>
<td>0.874</td>
<td>1.1</td>
<td>79.0</td>
<td>88.2</td>
<td>0.672</td>
<td>0.94</td>
</tr>
<tr>
<td>ADC*(0 to 1000)</td>
<td>0.882</td>
<td>1.5</td>
<td>72.6</td>
<td>100.0</td>
<td>0.726</td>
<td>0.94</td>
</tr>
<tr>
<td>ADC*(0 to 2000)</td>
<td>0.878</td>
<td>1.1</td>
<td>77.4</td>
<td>88.2</td>
<td>0.656</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Biexponential</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0.861</td>
<td>1.1</td>
<td>71.0</td>
<td>94.1</td>
<td>0.651</td>
<td>0.76</td>
</tr>
<tr>
<td>D*</td>
<td>0.643</td>
<td>22.2</td>
<td>88.2</td>
<td>56.5</td>
<td>0.447</td>
<td>&lt; 0.01</td>
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<tr>
<td>f</td>
<td>0.709</td>
<td>0.37</td>
<td>46.8</td>
<td>100.0</td>
<td>0.468</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>Stretched exponential</strong></td>
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<tr>
<td>DDC</td>
<td>0.841</td>
<td>2.0</td>
<td>59.7</td>
<td>100.0</td>
<td>0.597</td>
<td>0.53</td>
</tr>
<tr>
<td>α</td>
<td>0.748</td>
<td>0.73</td>
<td>62.9</td>
<td>88.2</td>
<td>0.511</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>Kurtosis DWI</strong></td>
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</tr>
<tr>
<td>Dapp</td>
<td>0.815</td>
<td>2.6</td>
<td>61.3</td>
<td>88.2</td>
<td>0.495</td>
<td>0.33</td>
</tr>
<tr>
<td>Kapp</td>
<td>0.889</td>
<td>0.65</td>
<td>100.0</td>
<td>74.2</td>
<td>0.742</td>
<td>0.84</td>
</tr>
</tbody>
</table>

AUC: Area under the receiver operating characteristic curve; ADC: Apparent diffusion coefficient; DWI: Diffusion-weighted imaging; D: Slow diffusion coefficient; D*: Fast diffusion coefficient; f: Fraction of fast diffusion; DDC: Distributed diffusion coefficient; α: Anomalous exponent term; Dapp: Mean diffusivity; Kapp: Mean kurtosis. The cut-off values for the ADC, D, D*, DDC, and Dapp are given in units of $\times 10^3$ mm$^2$/s. P values from statistical comparisons between the AUC values of the ADC*(0 and 1000) (Ref) and other diffusion parameters were obtained by using the method of Z test.

Regarding the perfusion-related metrics evaluated in our study, the f values of the malignant thyroid nodules were also significantly lower than those of benign thyroid nodules. However, Tan et al.[10] reported that the f values of malignant thyroid tumors were significantly higher than those of benign lesions. In 2007, Tezelman et al.[28] used dynamic contrast-enhanced (DCE) MRI to show that thyroid cancer had increased perfusion and blood volume compared with benign lesions. If perfusion is related to blood volume, the findings of their report are inconsistent with our evidence, which shows that the f value is significantly lower in thyroid cancer than in benign lesions. Our results with inconsistent perfusion values are also reflected by the results of other similar studies that have reported paradoxically lower f values in cancerous tissues[12,25-27]. A possible reason for this discrepancy may be explained by the theory that f values are not specific to perfusion alone but also be sensitive to other density phenomena[29]. Another possible reason is that f value is dependent on echo time (TE), at longer TE, the signal decays more at low b values, which would increase the estimated f values[30]. Hence, the lower f value in benign tumors may be related to parameters such as TE[30]. In the current study, the AUC of the f value was significantly lower than that of the ADC value obtained from the mono-exponential model. Although the mean D* value was slightly higher in malignant thyroid nodules than in benign thyroid nodules, the difference was not significant in our study. This finding is probably due to its sensitivity to noise, and the D* value has been shown to have poorer reproducibility than the f value in prior studies of the liver[14].

The stretched exponential diffusion model is an alternate method that can simultaneously assess both tissue heterogeneity and diffusion. Prior studies have reported that the stretched exponential diffusion model has better diagnostic performance for differentiating malignant from benign lesions than ADC parameters derived from a mono-exponential model in breast cancer and prostate cancer[31,32]. The DDC can be considered a weighted sum over a distribution of ADCs that represent multiexponential decay properties[31]. In our study, the DDC of the malignant thyroid nodule was significantly lower than that of benign thyroid nodules, but the results of the ROC curve analysis indicate that the diagnostic value of the DDC did not achieve a significant difference compared with ADC. The diffusion parameter α is supposed to represent intravoxel water diffusion heterogeneity. Values of α near 0 indicate high intravoxel diffusion heterogeneity. In our study, α was significantly lower in malignant thyroid nodules than in benign thyroid nodules, suggesting that malignant thyroid nodules exhibited higher intravoxel diffusion heterogeneity than the benign thyroid nodules. However, the diagnostic performance of α was lower than that of the ADC.
Recently, the potential utility of DKI using higher b values rather than conventional DWI has been reported for detecting pathological alterations in tissue diffusion properties in neural diseases and oncologic applications[33]. Our study showed that malignant thyroid lesions had significantly lower Dapp and higher Kapp values than benign lesions, similar to the results reported by Shi et al[34]. This finding might be because the malignant group had lesions with higher cell density than those in the benign group, which contributed to restriction of water diffusion in the extracellular space. Moreover, Shi et al[34] found that quantitative DKI was superior to conventional DWI because the Dapp value corrected by the DKI model showed a greater AUC than the ADC, and Kapp showed a higher sensitivity than the ADC. However, in our study, Kapp achieved the highest AUC of 0.889 with a higher sensitivity of 100% than ADC, but the diagnostic performance of those two parameters was not significantly different. Kapp may be a promising indicator with good diagnostic performance.

This study has several limitations. First, the study sample included was relatively small, especially the sample of patients with thyroid cancer, which is a possible reason that may account for the 100% sensitivity or specificity in the ROC curve analysis results. Our findings need to be validated in a larger and more heterogeneous cohort that includes a wider spectrum of thyroid tumor types. Second, regarding the patients in our study, the benign group included only patients with solid nodular goiter and thyroid adenoma, rather than those with all types of benign nodules. In addition, the malignant group did not include all types of thyroid cancer; thus, this may have resulted in some selection bias because of histopathological heterogeneity of thyroid nodules. Third, we selected only the solid regions of the lesion instead of the entire lesion, which may have resulted in some selection bias because of histopathological heterogeneity.
Figure 2 Data from a 35-year-old male with a malignant nodule of follicular thyroid carcinoma in the right lateral of thyroid. A: T2WI shows the lesion in the right lateral of thyroid (orange arrow). Multiparametric diffusion parameter maps fitted by mono-exponential (B = ADC\(_{0 \text{ and } 1000}\), C = ADC\(_{0 \text{ to } 1000}\), D = ADC\(_{0 \text{ and } 2000}\), E = ADC\(_{0 \text{ and } 2000}\)), bi-exponential (F = D; G = D\(^*\); H = f), stretched exponential (I = DDC; J = \(\alpha\)), and kurtosis diffusion-weighted imaging (K = Dapp; L = Kapp) models show the lesion in the right lateral of thyroid (orange arrow); M: Histopathological H&E image (original magnification, 40×) demonstrate high cell density (stars) and capsular invasion (write arrow); N: Plot of the decay of diffusion weighted signal intensity fitted by a mono-exponential (green), biexponential (blue), stretched-exponential (dark), and kurtosis (red) models for the nodule; O: Plot of the decay of diffusion weighted signal intensity fitted by a mono-exponential with \(b = 0\) and 1000 (dark), \(b = 0\) to 1000 (red), \(b = 0\) and 2000 (blue), and \(b = 0\) to 2000 (green) for the nodule. ADC: Apparent diffusion coefficient; D: Slow diffusion coefficient; D\(^*\): Fast diffusion coefficient; f: Fraction of fast diffusion; DDC: Distributed diffusion coefficient; \(\alpha\): Anomalous exponent term; Dapp: Mean diffusivity; Kapp: Mean kurtosis; ROC: Receiver operating characteristic.

Figure 3 Receiver operating characteristic curve analysis of different diffusion parameters for differentiating malignant thyroid nodules from benign thyroid nodules. ADC: Apparent diffusion coefficient; D: Slow diffusion coefficient; D\(^*\): Fast diffusion coefficient; f: Fraction of fast diffusion; DDC: Distributed diffusion coefficient; \(\alpha\): Anomalous exponent term; Dapp: Mean diffusivity; Kapp: Mean kurtosis; ROC: Receiver operating characteristic.
CONCLUSION

In conclusion, our study demonstrates the following: (1) Multiple diffusion coefficient parameters obtained by fitting with mono-exponential, bi-exponential, stretched exponential, and kurtosis DWI models are feasible techniques for investigating thyroid nodules; (2) The metrics including D, DDC, Dapp and Kapp provide additional information with similar diagnostic performance of ADC, and combination of these metrics may contribute to differentiate benign and malignant thyroid nodules; and (3) the ADC calculated with a mono-exponential model using a single pair of conventional b values (b = 1000 s/mm²) have similar diagnostic performance to those calculated with higher b values (b value > 1000 s/mm²). Clinically, therefore, for the institution has ability to generate higher b values for DWI, the metrics of D, DDC, Dapp and Kapp could be evaluated, which might provide additional information; otherwise, using a single pair of conventional b values (b = 1000 s/mm²) still remained a valuable diffusion parameter for differentiating malignant thyroid nodules from benign thyroid nodules.

ARTICLE HIGHLIGHTS

Research background
The value of multiparameter diffusion-weighted imaging (DWI) in quantitative evaluation of thyroid nodule has not been clarified.

Research motivation
It provides a new idea for differentiating benign and malignant thyroid results by using multiparametric diffusion-weighted imaging.

Research objectives
To provide a non-invasive diagnostic means for differentiating benign and malignant thyroid nodules by multiparametric DWI, furthermore, we elucidated which parameters have diagnostic function in differentiating the nature of thyroid nodule.

Research methods
We obtained Multiple DWI parameters by patients who underwent multi-b value diffusion-weighted imaging of the thyroid, then the data of benign and malignant nodules were obtained and analyzed.

Research results
Malignant lesions displayed lower diffusion parameters including apparent diffusion coefficient (ADC), the true diffusion coefficient (D), the perfusion fraction (f), the distributed diffusion coefficient (DDC), the intravoxel water diffusion heterogeneity (α) and kurtosis model-derived ADC (Dapp), and higher apparent diffusional kurtosis (Kapp) than benign entities (all P < 0.01). The area under the ROC curve (AUC) of the ADC calculated with a mono-exponential model (b = 1000 s/mm²) was significantly higher than the AUC of D, f and α (all P < 0.05) for differentiating benign from malignant lesions.

Research conclusions
The metrics including D, DDC, Dapp and Kapp provide additional information with similar diagnostic performance of ADC, combination of these metrics may contribute to differentiate benign and malignant thyroid nodules.

Research perspectives
In the future, multiple parameters of magnetic resonance diffusion can be used to accurately distinguish benign and malignant thyroid nodules.

FOOTNOTES

Author contributions: Zhu X and Han J designed the research study; Wang J and Wang YC performed the research; Zhu ZF and Tang J contributed software and formal analysis; Wen XW and Fang Y analyzed the data; Zhu X and Han J wrote the manuscript; all authors have read and approve the final manuscript.

Supported by the Health Commission of Zhejiang Province, No. 2019KY690.

Institutional review board statement: The study was reviewed and approved by the First Hospital of Jiaxing Research and Ethics Committee [(Approval No.2017-226)].

Clinical trial registration statement: The clinical trial is registered with Chinese Clinical Trial Registry, using identifier

**Informed consent statement:** All study participants, or their legal guardian, provided written consent prior to study enrollment.

**Conflict-of-interest statement:** All the authors declare no conflict of interest.

**Data sharing statement:** No additional data are available.

**CONSORT 2010 statement:** The authors have read the CONSORT Statement—checklist of items, and the manuscript was prepared and revised according to the CONSORT Statement—checklist of items.

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S-Editor: Liu JH

L-Editor: A

P-Editor: Liu JH

REFERENCES


Zhu X et al. Quantitative differentiation of malignant and benign thyroid nodules

[PMID: 27284961 DOI: 10.1002/jmri.25327]


Randomized Controlled Trial

Application of unified protocol as a transdiagnostic treatment for emotional disorders during COVID-19: An internet-delivered randomized controlled trial

Kou Yan, Mohammad Hassan Yusufi, Nabi Nazari

**Abstract**

**BACKGROUND**
The coronavirus disease 2019 (COVID-19) pandemic has been an emotionally challenging time, especially for young adults. It is associated with a substantial increase in the prevalence of mental health problems, negative symptoms, and stressful experiences that compromise well-being. In low-income countries, internet-delivered psychological services could have a remarkable impact on the population's mental health, given the lack of mental health professionals.

**AIM**
To investigate the efficacy of internet-delivered cognitive-behavior therapy (CBT)-transdiagnostic intervention for adults with emotional disorders.

**METHODS**
In this internet-delivered randomized controlled trial, 102 students with an emotional disorder (mean age = 28.20 years, standard deviation = 5.07) were randomly allocated to receive unified protocol (UP) ($n = 51$) or treatment as the usual intervention. Following a semi-structured clinical interview, participants completed an online survey including the Overall Anxiety Severity and Impairment Scale, Overall Depression Severity and Impairment Scale, Difficulties in Emotion Regulation Scale, Positive and Negative Affect Schedule, and Emotional Style Questionnaire.
RESULTS
The participants showed a high degree of adherence. In total, 78% (n = 40) of the experimental group participants completed the UP treatment. Considering the intention to treat procedure, the results of the analysis of covariance indicated that participants who received UP showed statistically significant changes in depression symptoms (Cohen's $d = -1.50$ with 95% confidence interval (CI): -1.90 to -1.10), anxiety (Cohen's $d = -1.06$ with 95%CI: -1.48 to -0.65), difficulties with emotion regulation (Cohen's $d = -0.33$ with 95%CI: -0.7 to -0.06), positive affect (Cohen's $d = 1.27$ with 95%CI: 0.85 to 1.68), negative affect (Cohen's $d = -0.04$ with 95%CI: -1.46 to -0.63), and healthy emotionality (Cohen's $d = 0.53$ with 95%CI: 0.09 to 0.13) compared with the control group.

CONCLUSION
This study’s findings highlight the potential value of transdiagnostic internet-delivered programs for young adults with an emotional disorder during the COVID-19 pandemic, and expand the research examining emotional well-being improvements resulting from CBT-transdiagnostic interventions. The findings suggest that UP, which generally concentrates on reducing negative effects, can increase positive effects.

Key Words: Unified protocol; COVID-19; Internet-delivered; Emotion regulation; Transdiagnostic; Depression; Anxiety

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Core Tip: Transdiagnostic treatments may optimize mental health services during the current pandemic. The findings of this study highlight the potential value of transdiagnostic internet-delivered programs for adults. The unified protocol is a promising transdiagnostic treatment for youth with emotional disorders during the coronavirus disease 2019 pandemic. The study’s findings expand the body of research examining positive affect improvements resulting from cognitive-behavior therapy-transdiagnostic interventions.

URL: https://www.wjgnet.com/2307-8960/full/v10/i24/8599.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i24.8599

INTRODUCTION
Depressive and anxiety disorders are highly prevalent conditions associated with significant impairments across all areas of life and great economic costs[1]. Before the coronavirus disease 2019 (COVID-19) outbreak, depressive and anxiety disorders were ranked as leading health burdens worldwide. Epidemiological studies have estimated a significant increase in the prevalence of major depressive disorders during the COVID-19 pandemic[2,3]. The COVID-19 outbreak has contributed to severe medical and mental health issues, particularly in vulnerable groups (e.g., students and individuals with preexisting mental health problems)[4], with devastating morbidity and mortality[5,6]. Emotional disorders (e.g., depression, anxiety, trauma-related, and somatic symptom disorders) are characterized by intense and unpleasant negative emotions and aversive reactions to these affective experiences, triggered by a reduced sense of emotion regulation[7]. These conditions are also comorbid and commonly coexist during the lifespan. For example, 45.7% of patients with major depressive disorder present one or more anxiety disorders[8]. The current pandemic has generated frequent and intense negative emotions[9]. Research indicates that psychiatric comorbidities or multiple co-occurring mental health problems are highly prevalent during the pandemic[10,11]. Traditional treatments or specific disorder protocols that target one diagnosis at a time (e.g., major depressive disorder) may be difficult to rationalize when the clinical reality is suspected to be effective in cases with high rates of comorbidity[12]. Specific disorder treatments for primary depression are not equipped to handle comorbid conditions[13] and typically fail to produce significant outcomes in comorbid anxiety symptomatology[14]. As an alternative approach, the development of innovative transdiagnostic therapies reflects a shift from focusing on the distinctions between conditions to similarities and shared mechanisms[15].
The term transdiagnostic reflects an underlying psychological construct causally linked to the class of disorders mechanistically[16]. In the context of treatment approaches, transdiagnostic interventions focus on targeting the shared or common mechanisms implicated in the etiology or onset or maintenance of a group of disorders[17-19]. Neuroticism is a personality trait or temperamental characteristic closely linked to the emergence of anxiety and depression and the genetic risk of developing various mental and physical illnesses. Individual differences in neuroticism predict a broad range of adverse physical and psychological outcomes[20,21], such as depression[22], anxiety, and somatic symptoms[23]. Neuroticism has also been shown to be a strong predictor of internalizing symptomology during the pandemic[24].

Additionally, emotion dysregulation is a core feature of almost every major form of psychopathology diagnosis with comorbidity[25]. Individuals with emotional disorders report higher impairment in emotion regulation, including maladaptive coping strategies and reduced awareness[26]. Other contributing factors with transdiagnostic relevance mechanisms are anxiety sensitivity, intolerance uncertainty, and rumination, observed in individuals during the pandemic[27]. The dissemination and implications of integrative transdiagnostic treatments are essential to target neuroticism or emotion dysregulation, particularly during the current pandemic[28].

The unified protocol (UP), a manualized, evidence-based, cognitive-behavior therapy (CBT)-transdiagnostic, emotion-focused treatment for emotional disorders[29,30], represents an intervention explicitly developed to address temperamental vulnerabilities, in this case, neuroticism and difficulties in emotion regulation comorbid conditions. UP, with its emphasis on common neurotic processes (e.g., avoidance of effective experience)[31], has the potential to facilitate training programs and address issues regarding generalizability to everyday clinical settings. Evidence represents the equivalence between UP and gold standard protocols for patients with depression and anxiety[32]. An increasing number of studies have supported the effectiveness of UP in reducing anxiety[33] and depression symptoms[34]. With COVID-19 continuing to spread around the globe, scholars anticipate a substantial increase in the rates of depression and anxiety as individuals face emotional challenges. Concerning the substantial increase in the prevalence of depression and anxiety, psychological comorbidities, and negative affective experiences (i.e. related to unemployment, isolation) during the current pandemic, the application of UP could be beneficial by targeting the core features of emotional disorders such as neuroticism[35] and emotion dysregulation mechanisms[36]. As such treatments tackle multiple problems and can facilitate dissemination and training using a single set of intervention protocols, they provide a more parsimonious and practical approach[37,38]. However, there is a lack of experimental data on the UP and COVID-19.

Restricting policies (e.g., physical distancing) to minimize the risk of infection have made it more difficult to seek treatment. However, individuals have difficulty accessing appropriate intervention, and the COVID-19 pandemic exacerbates this. Digital mental health services (i.e. internet-delivered) offer the possibility of expanding the accessibility of mental health care[39]. Nevertheless, meta-analysis findings have shown that internet-based therapies are effective for anxiety and depression[40-42], with moderate to high mean effect sizes. Recent research has demonstrated that internet-based cognitive-behavioral therapies are acceptable to college students and effectively lower anxiety and depression symptoms[43]. Compared with traditional face-to-face interventions, internet-delivered interventions provide widespread access and dissemination and increase cost-effectiveness. Evidence has revealed that internet-delivered interventions are as efficacious as traditional face-to-face treatments[44,45]. Transdiagnostic, emotion-focused cognitive-behavioral treatments, such as UP for Transdiagnostic Treatment of Emotional Disorders (UP), may be particularly well suited to address the challenges practicing psychologists and their patients face during the current COVID-19 pandemic[46-48].

**Current study**

This study was conducted to examine the application of an internet-delivered CBT-transdiagnostic intervention for adults with emotional disorders. It was hypothesized that participants randomly assigned to receive UP would demonstrate significant changes in depression, anxiety, affectivity (positive and negative affects), emotion dysregulation, and healthy emotionality compared with randomly assigned participants to the treatment-as-usual group (TAU). In addition, it was hypothesized that the experimental group participants would demonstrate significant changes in the dependent variable scores compared with baseline at post-intervention.

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**MATERIALS AND METHODS**

**Sample**

A total of 170 students were screened, and 102 were eligible to participate in the trial. Sixty-eight individuals were excluded from this study. Of these, thirty-eight students declined or were uninterested (without a specific reason) in participating in the study. The consort diagram is shown in Figure 1. The CONSORT 2010 checklist of information was used to report a randomized trial (Supplementary material)[49]. Individuals were eligible if they met the following criteria: aged 18 years or older with no prior...
experience with UP, were willing to participate and were randomly assigned to the control condition, had access to the internet and had an e-mail address, were fluent in Persian, and met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria for depression or anxiety disorders [50, 51]. Individuals were excluded if they met the following criteria: Presence of a severe condition that would require prioritization for treatment (e.g., schizophrenia, psychosis); pregnancy or breastfeeding; clear and current or history of substance dependence disorder or alcohol, and suicide; and unstable medication regimens (e.g., complex medication regimens to manage their health; unstable dose of medication over the last 3 months). The study was reviewed and approved by the internal review board of Bamyan University (Bamyan, Afghanistan). Informed consent was obtained from all subjects involved in the study.

**Measures**

The survey comprised the Overall Anxiety Severity and Impairment Scale (OASIS) [52], Overall Depression Severity and Impairment Scale (ODSIS) [53], Difficulties in Emotion Regulation Scale Short Form (DERS-SF) [54], Positive and Negative Affect Schedule (PANAS) [55], and Emotional Style Questionnaire (ESQ) [56]; Persian version [57]). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV-TR) [58] is a semi-structured interview that evaluates diagnostic criteria. At baseline, interviews were conducted to evaluate the participants to investigate the inclusion and exclusion criteria.

**Primary outcomes**

**Anxiety:** The OASIS is a brief unidimensional transdiagnostic self-report scale developed to assess anxiety symptoms and impairment severity. Respondents rated the five items on a scale ranging from 0 (never) to 4 (extreme or all the time). Additionally, it can be used to measure anxiety disorders with comorbidities and sub-threshold anxiety symptoms. The scale had very good internal consistency (Cronbach’s $\alpha = 0.86$).

**Depression:** The ODSIS is a brief unidimensional transdiagnostic self-report scale. The ODSIS is a direct adaptation of the OASIS and has been modified to assess depression. The ODSIS is a brief, five-item questionnaire that assesses dimensional depression-related symptom severity and can be used across depressive disorders with varied comorbidities. Participants rated the five items on a scale ranging from 0 (never) to 4 (extreme or all the time). The scale had very good internal consistency (Cronbach’s $\alpha = 0.87$).

**Secondary outcomes**

**Affectivity:** The PANAS was employed to determine the pleasant (ten descriptors) and unpleasant (ten descriptors) feelings experienced over the past month. Participants rated the items on a five-point scale,
ranging from very slightly (1) to extremely (5). The scale had very good internal consistency (α = 0.83).

**Difficulties in emotion regulation:** The DERS-SF was used to measure emotional dysregulation. The respondents rated the 18 items on a five-point scale, ranging from 1 (almost never) to 5 (almost always). Higher scores indicate greater difficulties in emotion regulation. The scale had very good internal consistency (Cronbach’s α = 0.81).

**Healthy emotionality:** The ESQ was used to measure healthy emotionality. Respondents rated each 24-item item on a seven-point scale ranging from 1 (strongly disagree) to 7 (strongly agree). Raw scores range from 24 to 168, with higher scores indicating higher adaptive emotional functioning. The scale had very good internal consistency (Cronbach’s α = 0.89).

### Procedure

The current study was an internet-based, two-armed, accessor-blinded, parallel randomized controlled trial (RCT) comparing the application of an online intervention (UP) with an online TAU control group. The study (e.g., all assessments and treatments) was administered via the internet in a university setting, including an intervention platform. The study was conducted during the COVID-19 pandemic (August 2020 to January 2021). Over 3 mo, participants were recruited through online announcements, flyers, and referrals. Additionally, the link for the study was distributed and posted on online community platforms such as university forums. Potentially eligible individuals who applied to participate in the RCT were informed of the study’s objectives, advantages, hazards, session numbers, confidentiality, assurances of anonymity, and the possibility of group assignment via e-mail or telephone. Participants were informed that they could withdraw their consent or stop participating at any point in the study. Also, they were free to skip specific questions and continue to participate.

Individuals who initially obtained a high score (greater than 15) on the Beck Anxiety Inventory[59] were requested to obtain informed consent. The consented participants underwent an interview to ensure that the eligibility criteria were fulfilled. Two clinical psychologists evaluated the participants' personal history, mental status, personal resources, and suicide risk through clinical interviews through 45 min of online video communication. Individuals who met the SCID-I-IV criteria for depression or anxiety disorders were requested to rate primary and secondary outcomes. The participants rated the primary and secondary outcomes at two time points: Time 1: Pre-treatment to allocation, including baseline; and Time 2: Immediately after the intervention, including posttreatment assessment. The intervention schedule is presented in Table 1.

### Sample size

Using G*Power software[60], a power analysis was suggested in an analysis of covariance (ANCOVA) design assuming the desired α level of 0.05, a power level of 0.8, two groups, and two measurement levels to detect a medium to large effect size[32,61]. The sample size was 82. Considering the reported dropout rate of 25%[62], the required sample size was 102.

### Randomization and blinding procedures

The participants were randomly allocated to the intervention groups using the permuted block technique. An independent statistician generated the allocation schedule. Random sequence block sizes were generated using a computer random number generator with an equal allocation ratio. The statistician informed the observer staff and participants of the random allocation results via e-mail. The psychological evaluators, statisticians, and assessors who measured and recorded the data were blinded to the conditions and the participants’ groups. Participants were instructed not to share any assigned conditions or diagnostic status data.

### Interventions

**Experimental group:** The UP is typically delivered over 12 to 14 sessions in a group format[63]. UP is a modular intervention that was administered and structured based on manuals published by Barlow et al[29,30,32]. UP comprises eight different treatment modules delivered in twelve 2-h weekly sessions. The UP comprises five core modules: present-focused awareness, cognitive flexibility, changing emotional behaviors, awareness and tolerance of physical sensations, and emotional exposure. A module precedes these five core modules on motivation and readiness for change and treatment engagement. Also, the second introductory module provides psychoeducation and a framework for tracking emotional experiences. After the five core modules were completed, the final module for relapse prevention was provided. Table 2 presents an overview of each module's content and intervention schedule (Supplementary material for a more thorough explanation).

**Control group:** The control group received TAU as provided by the general practitioners. TAU is considered non-treatment and/or practical advice by general practitioners administered in normal care, focusing on reducing unpleasant feelings and negative emotional symptomatology. TAU was delivered in twelve 2 h weekly sessions. The participants who received the introductory modules of UP included four psychoeducation sessions. Specifically, the TAU comprises three parts: four sessions of psychoedu-
Table 1 Study schedule of enrollment, intervention, and assessment

<table>
<thead>
<tr>
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<th>Enrollment</th>
<th>Pre-allocation</th>
<th>Allocation</th>
<th>Post-intervention</th>
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<tr>
<td>Duration</td>
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<td>12 wk</td>
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<td>Eligibility</td>
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<td>Intervention</td>
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<td>OASIS</td>
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<td>ODSIS</td>
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<tr>
<td>Secondary outcomes</td>
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<td>DERS</td>
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<tr>
<td>ESQ</td>
<td>x</td>
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<tr>
<td>PANAS</td>
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</table>

*: Completed at this stage; -: Intervention period. DERS: Difficulties in Emotion Regulation Scale; ESQ: Emotional Style Questionnaire; OASIS: Overall Anxiety Severity and Impairment Scale; ODSIS: The Overall Depression Severity and Impairment Scale; PANAS: Positive and Negative Affect Schedule.

Table 2 Content and the number of sessions for each module

<table>
<thead>
<tr>
<th>Module</th>
<th>Schedule</th>
<th>Content and the number of sessions for each module</th>
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<tbody>
<tr>
<td>One</td>
<td>Week 1</td>
<td>Setting goals and maintaining motivation (1 session)</td>
</tr>
<tr>
<td>Two</td>
<td>Week 2</td>
<td>Understanding emotions (1 session)</td>
</tr>
<tr>
<td>Three</td>
<td>Week 3 and 4</td>
<td>Mindful emotion awareness (2 sessions)</td>
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<tr>
<td>Four</td>
<td>Week 5</td>
<td>Cognitive flexibility (2 sessions)</td>
</tr>
<tr>
<td>Five</td>
<td>Week 6</td>
<td>Countering emotional behaviors (1 sessions)</td>
</tr>
<tr>
<td>Six</td>
<td>Week 7</td>
<td>Understanding and confronting physical sensations (1 session)</td>
</tr>
<tr>
<td>Seven</td>
<td>Weeks 8 to 11</td>
<td>Emotion exposures (5 sessions)</td>
</tr>
<tr>
<td>Eight</td>
<td>Week 12</td>
<td>Recognizing accomplishments and looking to the future (1 session)</td>
</tr>
</tbody>
</table>

1The modules of three, four, five, six, and seven are core modules.
2The modules of one and two are introductory modules.
3The module of eight is the relapse introductory module.

Education, four sessions of COVID-19 consideration, and four sessions of sharing experiences.

Risk
For participants with higher concerns related to psychological states, support was delivered by clinical psychologists and general practitioners via e-mail and telephone. Clinical team members received a comprehensive refreshment course in the context of psychological assessments, structured interviews, and ethics in clinical research.

Statistical analysis
Data were analyzed using SPSS with a two-sided 5% significance level. Based on the intent-to-treat procedure, the data for all randomized participants were considered in the final analysis. The last observation-carried-forward method was considered the next point for dropping data to handle missing
data. Descriptive statistics were utilized to present the means and standard deviation for continuous variables and numbers or percentages for categorical variables. The parametric test of ANCOVA was performed to investigate UP efficacy compared with TAU, with the time1 (baseline) collected data as covariate scores to control preexisting group differences. The paired \( t \)-test was conducted to investigate within-group changes. Effect sizes are reported as partial eta-squared. Also, the standardized effect size (Cohen’s \( d \)) was calculated for pretreatment and posttreatment changes based on the means and standard deviations. Effect size values were interpreted conservatively, with 0.2, 0.5, and 0.8 reflecting small, medium, and large treatment effects[64].

**RESULTS**

**Descriptive characteristics**

The baseline characteristics of the study participants are presented in Table 3. At baseline, independent \( t \)-tests showed no significant group differences in age, primary outcomes, or secondary outcomes \( (P > 0.05) \), indicating successful randomization. The sample comprised 102 adults aged 20 years to 39 years. The mean age was 28.07 years \([\text{standard deviation (SD)} = 5.07]\). At the end of the study, 78\% \((n = 40)\) of the experimental group participants completed UP treatment sessions and completed the assessment protocol. Additionally, 37\% \((n = 20)\) of participants left the control group. In total, 70\% \((n = 71)\) of the participants completed the course.

**Treatment results**

Table 4 shows the results of the parametric test of ANCOVA to compare the effectiveness of the unified protocol intervention with TAU at posttreatment (Time 2). At the end of the study, the ANCOVA results revealed that students who received the UP intervention had a statistically significant reduction in ODISIS score compared with those who received TAU; Cohen’s \( d = -1.50 \) with 95% CI: -1.90 to -1.06; mean different = 4.08, standard error (SE) = 0.52, \( P < 0.001 \), with 95% CI: 3.05 to 5.11. ANCOVA results also revealed that students who received UP intervention demonstrated a statistically significant reduction in OASIS score compared with those who received TAU, Cohen’s \( d = -1.06 \) with 95% CI: -1.48 to -0.65; mean different = 2.47, SE = 0.56, \( P < 0.001 \), with 95% CI: 1.39 to 3.56.

At the end of the study, the results of ANCOVA revealed that students who received UP intervention demonstrated a statistically significant reduction in DERS score compared with those who received TAU; Cohen’s \( d = -0.33 \) with 95% CI: -0.7 to -0.06; mean different = 4.19, SE = 1.63, \( P = 0.01 \), with 95% CI: 0.95 to 7.43. ANCOVA results also revealed that students who received the UP intervention demonstrated a statistically significant increase in ESQ score compared with those who received TAU, Cohen’s \( d = 0.53 \), 95% CI: 0.14 to 0.93; mean different = 0.876, SE = 2.44, \( P = 0.001 \), with 95% CI: -13.56 to -3.92.

At the end of the study, the results of ANCOVA also revealed that students who received UP intervention demonstrated a statistically significant increase in PANAS-PA score compared with those who received TAU; Cohen’s \( d = 1.27 \) with 95% CI: 0.85 to 1.68; mean different = -4.41, SE = 0.69, \( P < 0.001 \), with 95% CI: -5.79 to -3.04. ANCOVA results also revealed that students who received UP intervention demonstrated a statistically significant reduction in PANAS-NA score compared with those who received TAU; Cohen’s \( d = -1.04 \) with 95% CI: -1.46 to -0.63; mean different = 3.72, SE = 0.81, \( P < 0.001 \), with 95% CI: 2.14 to 5.37. Means and SDs are presented at Time 1 and 2 (Table 5).

The paired \( t \)-test was conducted to calculate the within-group effect size post-intervention compared with baseline. These findings revealed that the experimental group participants significantly demonstrated improvement in the dependent variable scores post-intervention (Table 6). The results showed no significant differences for the control group participants between Time 2 and Time 1.

**DISCUSSION**

The outbreak of COVID-19 is an emotionally challenging time, especially for young adults, and is associated with a range of mental health problems, negative emotions, and stressful experiences that compromise a well-being. However, little evidence is available. The study was conducted to examine the application of an internet-delivered CBT-trans-diagnostic intervention for adults with emotional disorders. The study’s findings show that an internet-delivered CBT-trans-diagnostic intervention for adults with emotional disorders is an effective intervention for individuals with depression and anxiety during COVID-19. At posttreatment, the students who received the UP intervention showed significant changes in depression, anxiety, emotion dysregulation, affectivity, and healthy emotionality outcomes compared with those who participated in the TAU intervention. Our findings revealed significant changes in depression, anxiety, worry, emotion regulation, and affectivity measures in the unified protocol group posttreatment relative to baseline. There were no significant changes in the dependent variables in the control group at posttreatment relative to baseline. The stressful pandemic situations may have been a confounding factor that may have elevated mental health problems and higher than usual daily psychological life conditions. Therefore, the effectiveness of the intervention should be assessed in a larger sample size.
Table 3 Demographic characteristics of the sample, \( n = 102 \)

<table>
<thead>
<tr>
<th>Item characteristic</th>
<th>Baseline value</th>
<th>Control group value</th>
<th>UP group value</th>
<th>Test</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline value</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control group value</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UP group value</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Categorical variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex, ( n ) (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>48 (47.1)</td>
<td>21</td>
<td>27</td>
<td>( \chi^2 = 0.35 )</td>
<td>0.55</td>
</tr>
<tr>
<td>Man</td>
<td>54 (52.9)</td>
<td>30</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Principal diagnosis, ( n ) (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>45 (44.1)</td>
<td>22</td>
<td>23</td>
<td>( \chi^2 = 1.41 )</td>
<td>0.23</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>57 (55.9)</td>
<td>26</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Marital status, ( n ) (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>34 (33.3)</td>
<td>20</td>
<td>14</td>
<td>( \chi^2 = 11.33 )</td>
<td>0.001</td>
</tr>
<tr>
<td>In relationship</td>
<td>68 (66.7)</td>
<td>35</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychological disorders, ( n ) (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>40 (48.6)</td>
<td>18</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysthymia</td>
<td>5 (7.1)</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAD</td>
<td>34 (31.4)</td>
<td>15</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAD</td>
<td>23 (12.9)</td>
<td>11</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Continues variables (mean ± SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>28.07 ± 5.07</td>
<td>27.92 ± 4.67</td>
<td>28.18 ± 5.49</td>
<td>( t(100) = 0.28 )</td>
<td>0.77</td>
</tr>
<tr>
<td>Anxiety</td>
<td>11.14 ± 1.88</td>
<td>11.35 ± 2.05</td>
<td>10.88 ± 1.69</td>
<td>( t(100) = 1.26 )</td>
<td>0.21</td>
</tr>
<tr>
<td>Depression</td>
<td>10.97 ± 3.75</td>
<td>11.24 ± 1.75</td>
<td>10.71 ± 1.70</td>
<td>( t(100) = 1.09 )</td>
<td>0.26</td>
</tr>
<tr>
<td>Emotion dysregulation</td>
<td>49.69 ± 7.92</td>
<td>49.08 ± 7.10</td>
<td>50.18 ± 8.04</td>
<td>( t(100) = 0.80 )</td>
<td>0.4</td>
</tr>
<tr>
<td>Positive affect</td>
<td>26.49 ± 3.80</td>
<td>26.88 ± 3.92</td>
<td>26.10 ± 3.66</td>
<td>( t(100) = 1.05 )</td>
<td>0.29</td>
</tr>
<tr>
<td>Negative affect</td>
<td>27.44 ± 3.42</td>
<td>26.59 ± 3.66</td>
<td>27.74 ± 3.01</td>
<td>( t(100) = 1.48 )</td>
<td>0.14</td>
</tr>
<tr>
<td>Healthy emotionality</td>
<td>59.84 ± 8.82</td>
<td>60.33 ± 9.46</td>
<td>58.90 ± 11.35</td>
<td>( t(100) = 1.67 )</td>
<td>0.09</td>
</tr>
</tbody>
</table>

GAD: Generalized anxiety disorder; MDD: Major depressive disorder; SAD: Social anxiety disorder; SD: Standard deviation; \( t \): Independent \( t \)-test; UP: Unified protocol.

distress among the control group participants.

As an emotion-focused intervention, the core modules of UP are relevant to depression and anxiety. The improvement of emotion regulation can be associated with improved depression and anxiety symptoms[65,66]. A large body of evidence has examined the relationships and influences of emotional regulation in the treatment of depression[34,67,68], anxiety disorders[69,70], psychological distress[71], and rumination[72]. Depressed individuals lack emotional regulation skills, which results in higher rumination, avoidance, and suppression of positive emotion[73]. Individuals with higher depression report more ineffective coping strategies (e.g., rumination, self-blame) and a lower prevalence of adaptive emotion regulation behaviors (e.g., positive reappraisal, acceptance) when experiencing negative emotions[75]. Moreover, psychological distress is associated with maladaptive or ineffective reappraisal functions and mood fluctuations, which contribute to depression, anxiety, and mental health problems[76].

The study revealed surprising findings. Large effect sizes were found in the negative and positive effects, with a greater effect on positive affect than negative affect. The decrease in negative affect scores confirms the UP protocol’s theory that a mechanistically transdiagnostic treatment explicitly targets and reduces negative effects[19] as a psychopathology mechanism associated with the etiology of emotional disorders[77]. Despite the benefits of targeting positive emotions for physical and emotional well-being, most psychological interventions focus on targeting negative affect. Consequently, trans-diagnostic interventions for emotional disorders (e.g., UP) remain focused on evaluating outcomes of reduced negative affectivity symptoms. While UP initially focuses on reducing negative affect. A few investigations have revealed that the UP application may also promote positive affect[33,78,79]. Anxiety and depression have also been associated with lower levels of positive affect (i.e. extraversion) and a lower tendency to experience the world in an energetic and sociable way[80]. The study’s findings expand the
Table 4 Analysis of covariance at Time 2 to compare the unified protocol with treatment as usual

<table>
<thead>
<tr>
<th>Measure</th>
<th>Condition</th>
<th>Adjusted mean</th>
<th>Levene’s test</th>
<th>ANCOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TAU (1, 100)</td>
<td>Sig</td>
<td>F (1, 99)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Time 2</td>
<td>11.81</td>
<td>3.67</td>
<td>0.058</td>
</tr>
<tr>
<td>Depression</td>
<td>Time 2</td>
<td>12.11</td>
<td>3.43</td>
<td>0.07</td>
</tr>
<tr>
<td>Emotion dysregulation</td>
<td>Time 2</td>
<td>52.44</td>
<td>2.34</td>
<td>0.12</td>
</tr>
<tr>
<td>Positive affect</td>
<td>Time 2</td>
<td>26.72</td>
<td>0.12</td>
<td>0.68</td>
</tr>
<tr>
<td>Negative affect</td>
<td>Time 2</td>
<td>27.01</td>
<td>1.87</td>
<td>0.17</td>
</tr>
<tr>
<td>Healthy emotionality</td>
<td>Time 2</td>
<td>58.83</td>
<td>0.19</td>
<td>0.68</td>
</tr>
</tbody>
</table>

ANCOVA: analysis of covariance; η²p: Partial eta square; R²: Adjusted R square; TAU: Treatment as usual; Time 2: Immediately after treatment; UP: Unified Protocol.

Table 5 Control group and intervention group

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control group (TAU), n = 51</th>
<th>Intervention group (UP), n = 51</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1</td>
<td>Time 1I</td>
</tr>
<tr>
<td>Anxiety</td>
<td>11.35 ± 2.05</td>
<td>11.75 ± 2.42</td>
</tr>
<tr>
<td>Depression</td>
<td>11.24 ± 1.75</td>
<td>12.08 ± 2.16</td>
</tr>
<tr>
<td>Emotion difficulties</td>
<td>49.07 ± 7.32</td>
<td>50.31 ± 8.40</td>
</tr>
<tr>
<td>Negative affect</td>
<td>26.59 ± 3.66</td>
<td>27.89 ± 3.74</td>
</tr>
<tr>
<td>Healthy emotionality</td>
<td>60.33 ± 9.46</td>
<td>59.47 ± 10.41</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. Time 1I: Posttreatment; TAU: Treatment as usual; UP: Unified protocol.

body of research that examines positive affect improvements resulting from CBT-transdiagnostic interventions. The findings are promising, as they suggest that UP can promote positive affect and healthy emotionality, the constructs linked with emotional well-being and flourishing[81,82].

The current study could develop the UP, consisting of five core modules supported by the introductory modules, to teach clients how to accept and experience emotional distress while responding to them in more adaptive ways. As the treatment progresses, thoughts, physical feelings, and behaviors are examined in-depth, emphasizing the dysfunctional emotion regulation strategies that the patient has developed over time. Psychoeducational modules have increased patients’ readiness and motivation for change and facilitated coping by developing knowledge about the components (i.e. behavioral, cognitive, and psychological) of emotions and their interaction. The UP core modules concentrate on skills and strategies to target deficits in emotion regulation and facilitate more adaptive responses[30]. Individuals with depression experience deficits in mindful awareness of their emotions and experiences, particularly for nonjudgmental awareness and allowing oneself to notice emotions without triggering a repetitive negative thinking process such as rumination[83,84]. There is also evidence that mindfulness is an effective strategy to facilitate inhibitory learning in exposure therapy. Mindfulness training is associated with decreased reliance on strategies such as rumination and over engagement and a greater ability to tolerate negative emotions[85]. Individuals affected by adverse events may misinterpret abnormal bodily sensations as severe condition warning signs[86]. Accurate knowledge concerning COVID-19 infection may inhibit an automatic fear response and suppress an
Table 6 Paired t-test and within-group effect size at post-intervention

<table>
<thead>
<tr>
<th>Item</th>
<th>Treatment as usual group</th>
<th>Unified protocol group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t(50)</td>
<td>P value</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.88</td>
<td>0.37</td>
</tr>
<tr>
<td>Depression</td>
<td>-1.89</td>
<td>0.06</td>
</tr>
<tr>
<td>Emotion difficulties</td>
<td>-0.98</td>
<td>0.33</td>
</tr>
<tr>
<td>Positive affect</td>
<td>0.12</td>
<td>0.8</td>
</tr>
<tr>
<td>Negative affect</td>
<td>-0.36</td>
<td>0.72</td>
</tr>
<tr>
<td>Healthy emotionality</td>
<td>0.53</td>
<td>0.6</td>
</tr>
</tbody>
</table>

initial emotional and bodily fear reaction[87,88]. The higher levels of self-awareness lead to a clear recognition of the triggering of negative effects and facilitate adaptive emotional functioning through mindful attention toward unpleasant bodily sensations[89]. As another UP component, interoceptive exposure (IE) was originally designed to target fearful reactions and anxious sensitivity toward bodily sensations linked with anxiety and fear generated by stressful experiences[90]. IE effectively reduces the fear of bodily sensations, treats anxiety sensitivity, and promotes self-regulated social interaction abilities[68].

The feasibility of the internet-delivered UP in a group setting was evaluated. While emotion dysregulation is linked to a lower desire to engage in the treatment, the sample is characterized as challenging to treat[91]. Overall, participants had a high degree of adherence, and the treatment was well tolerated. Previous studies have substantially improved patient engagement and clinical outcomes in the guided internet-delivered group interventions[92-94].

Limitations

The trial's findings must be viewed in light of several limitations. The participants were students who were so well educated, which may have aided individuals’ capacity to develop more UP and reduce generalizability. The next limitation was the anticipated dropout rate (25%), which was lower than the actual dropout rate (30%). With an interdisciplinary approach to attrition incorporating a range of technological, environmental, and individual factors, future studies may be required to explain participants’ adherence comprehensively and improve retention in internet-delivered interventions. The next limitation was that the lack of follow-up made it difficult to assess prevention effects. Additionally, the study had no follow-up. Therefore, it was not easy to assess the long-term effects. Further studies with larger sample sizes and longer follow-up periods are required to replicate the findings of this study. The SCID-I-IV application at enrollment and the end of the study was a strength of this research.

CONCLUSION

Despite the limitations, the findings developed the unified protocol as a promising transdiagnostic treatment for youth with emotional disorders during the COVID-19 pandemic. UP has the potential to simplify training efforts while also addressing concerns about generalizability to routine care settings. Addressing these current barriers to widespread dissemination and implementation of evidence-based practice treatments has implications for bridging the science-to-service gap. The present study’s findings provide further evidence of internet-delivered CBT transdiagnostic interventions for improvements in depressive and anxiety disorders. In the challenging emotional events generated by the COVID-19 pandemic, the UP may be particularly well-suited to help individuals manage their experienced emotional problems. Additionally, from a global mental health perspective, a unified transdiagnostic treatment can potentially serve as a promising intervention approach that would be more cost-effective and may help to increase the availability of evidence-based treatments for emotional disorders, affordability of dissemination of a single protocol vs multiple protocols, and a decreased need for clinical observations by trained health professionals[95].

Further studies are required to assess the cost-effectiveness and economic evaluations of internet-delivered UP with larger samples, as this has not yet been formally evaluated. There would be value in adding qualitative components into future trials to establish the acceptance of unified protocol interventions for clinicians and clients. With an interdisciplinary approach to attrition incorporating a range of technological, environmental, and individual factors, future studies may be required to comprehensively explain participants’ adherence and improve retention in internet-delivered interventions.
ARTICLE HIGHLIGHTS

Research background
Depressive and anxiety disorders represent one of the greatest burdens among human diseases worldwide. These emotionally difficult conditions often manifest as comorbidities. A growing body of evidence indicates that the trans-diagnostic approach for treating these disorders is safe, feasible, and efficient.

Research motivation
Restricted policies (e.g., physical distancing) to minimize the risk of infection have made it more difficult to seek and attend treatment. The majority of individuals with mental health problems remain untreated. Internet-based interventions can help to address existing barriers. Also, trans-diagnostic, emotion-focused cognitive-behavioral treatments, such as unified protocol (UP), may be particularly well suited to address the challenges practicing psychologists and their patients face during the current coronavirus disease 2019 (COVID-19) pandemic.

Research objectives
This study was conducted to examine the application of an internet-delivered cognitive-behavior therapy (CBT)-transdiagnostic intervention for adults with emotional disorders.

Research methods
In this internet-delivered two-armed, accessor-blinded, parallel randomized controlled trial, 102 students with an emotional disorder were randomly allocated to receive UP or treatment as the usual interventions. Following a semi-structured clinical interview, participants completed an online survey, including the Overall Anxiety Severity and Impairment Scale, Overall Depression Severity and Impairment Scale, Difficulties in Emotion Regulation Scale, Positive and Negative Affect Schedule, and Emotional Style Questionnaire.

Research results
The findings of the current trial highlight the considerable potential of internet-delivered CBT programs, such as the UP, in improving access to online psychotherapy for affected adults by the pandemic. Our findings revealed significant changes in depression, anxiety, worry, emotion regulation, and affectivity measures in the unified protocol group posttreatment relative to baseline. There were no significant changes in the dependent variables in the control group at posttreatment relative to baseline.

Research conclusions
Transdiagnostic treatments target shared mechanisms between disorders to facilitate change across diagnoses. Overall, the findings support that the unified protocol could be an additional efficient as a parsimonious, transdiagnostic treatment of emotional disorders for young adults with emotional disorders during the current pandemic.

Research perspectives
From a global mental health perspective, a unified transdiagnostic treatment can potentially serve as a promising intervention approach that would be more cost-effective and may help to increase the availability of evidence-based treatments for emotional disorders, affordability of dissemination of a single protocol vs multiple protocols, and a decreased need for clinical observations by trained health professionals. With an interdisciplinary approach to attrition incorporating a range of technological, environmental, and individual factors, future studies may be required to comprehensively explain participants’ adherence and improve retention in internet-delivered interventions.

FOOTNOTES

Author contributions: Nazari N made significant contributions to the conceptualization and methodology of the study, and writing of the original draft; Yan K made significant contributions to the design, software, methodology, and supervision of the study; Yusufi MH made significant contributions to the preparation, data curation, writing, and revision of the draft. All authors wrote, reviewed, and edited the manuscript.

Supported by Shaanxi Province Education Science “13th Five-Year” Planning Topic: Drama Teaching Method in Application of Research of Psychological Education of Primary School students, No. SGH17H472; and Research Team Cultivation Project of Xi’an Eurasia University: Regional Children’s Psychological Development Research, No. 2021XJTD.

Institutional review board statement: The study was carried out in accordance with the Declaration of Helsinki and
was approved and registered by the ethical and Human Subjects Review. The study was reviewed and approved by the (Bamyan University) Institutional Review Board [(Approval No: BAMAFGHEDU2019070)].

**Clinical trial registration statement:** This study is registered at [https://clinicaltrials.gov/ct2/show/NCT04498949](https://clinicaltrials.gov/ct2/show/NCT04498949). The registration identification number is NCT04498949.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Data sharing statement:** The datasets generated and/or analyzed during the current study are not publicly available due to (local policy considerations and limitations of ethical approval involving the patient data and anonymity) but are available from the corresponding author upon reasonable request.

**CONSORT 2010 statement:** The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

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S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Ma YJ

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**REFERENCES**


Kennedy SM, Bilek EL, Ehrenreich-May J. A Randomized Controlled Pilot Trial of the Unified Protocol for


39 Latti EG, Siles-Shields C, Graham AK. An overview of and recommendations for more accessible digital mental health services. Nat Rev Psychol 2022; 1 [DOI: 10.1038/s44459-021-00003-1]


Randomized Controlled Trial

High-flow nasal cannula oxygen therapy during anesthesia recovery for older orthopedic surgery patients: A prospective randomized controlled trial

Xiao-Na Li, Cheng-Cheng Zhou, Zi-Qiang Lin, Bin Jia, Xiang-Yu Li, Gao-Feng Zhao, Fei Ye

BACKGROUND
Hypoxemia is a common complication in older patients during postoperative recovery and can cause pulmonary complications. Therefore, reducing the incidence of postoperative hypoxemia is a clinical concern.

AIM
To investigate the clinical efficacy of high-flow nasal cannula oxygen (HFNCO) in the resuscitation period of older orthopedic patients.

METHODS
In this prospective randomized controlled trial, 60 older patients who underwent orthopedic surgery under general anesthesia were randomly divided into two groups: those who used conventional face mask and those who used HFNCO. All patients were treated with 60% oxygen for 1 h after extubation. Patients in the conventional face mask group were treated with a combination of air (2 L) and oxygen (2 L) using a traditional mask, whereas those in the HFNCO group were treated with HFNCO at a constant temperature of 34 °C and flow rate of 40 L/min. We assessed the effectiveness of oxygen therapy by monitoring the patients’ arterial blood gas, peripheral oxygen saturation, and postoperative complications.

RESULTS
The characteristics of the patients were comparable between the groups. One hour
after extubation, patients in HFNCO group had a significantly higher arterial partial pressure of oxygen (paO\textsubscript{2}) than that of patients in conventional face mask group (\textit{P} < 0.001). At extubation and 1 h after extubation, patients in both groups showed a significantly higher arterial partial pressure of carbon dioxide (paCO\textsubscript{2}) than the baseline levels (\textit{P} < 0.001). There were no differences in the saturation of peripheral oxygen, paO\textsubscript{2}, and paCO\textsubscript{2} between the groups before anesthesia and before extubation (\textit{P} > 0.05). There were statistically significant differences in paO\textsubscript{2} between the two groups before anesthesia and 1 h after extubation and immediately after extubation and 1 h after extubation (\textit{P} < 0.001). However, there were no significant differences in the oxygen tolerance score before leaving the room, airway humidification, and pulmonary complications 3 d after surgery between the two groups (\textit{P} > 0.05).

**CONCLUSION**

HFNCO can improve oxygen partial pressure and respiratory function in elderly patients undergoing orthopedic surgery under general endotracheal anesthesia. Thus, HFNCO can be used to prevent postoperative hypoxemia.

**Key Words:** Anesthesia recovery; High flow nasal cannula oxygen; Hypoxemia; Older patients; Orthopedic surgery; Pulmonary complications

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**Core Tip:** This prospective randomized controlled study involving 60 patients evaluated the effects of different oxygen delivery methods. Additionally, the study investigated the clinical efficacy of high-flow nasal cannula oxygen (HFNCO) on the recovery period of older orthopedic patients. The current results showed that HFNCO can improve oxygen partial pressure and respiratory function in older patients undergoing orthopedic surgery with general anesthesia under endotracheal intubation.

**Citation:** Li XN, Zhou CC, Lin ZQ, Jia B, Li XY, Zhao GF, Ye F. High-flow nasal cannula oxygen therapy during anesthesia recovery for older orthopedic surgery patients: A prospective randomized controlled trial. World J Clin Cases 2022; 10(24): 8615-8624


**DOI:** [https://dx.doi.org/10.12998/wjcc.v10.i24.8615](https://dx.doi.org/10.12998/wjcc.v10.i24.8615)

**INTRODUCTION**

With aging of the global population, the number of orthopedic surgeries required for older patients is increasing annually. With the advances in ultrasonography-guided nerve block technology, the combination of general anesthesia with nerve block is increasingly used in orthopedic surgeries for older patients. However, patients often present with hypoxemia when the tracheal tube is removed after surgery, due to pre-existing chronic diseases and a decline in organ reserve. Additionally, following general anesthesia, the clinical manifestations of inherent diseases and conditions, such as chronic obstructive pulmonary disease, slow anesthesia metabolism, and lung injury, become apparent again. Currently, the accepted diagnostic criterion for hypoxemia is saturation of peripheral oxygen (SpO\textsubscript{2}) \leq 90\%. The postoperative incidence of hypoxemia can reach 28\%-50\%. Hypoxemia may cause postoperative delirium and wound infection\cite{1}, and in severe cases, it may lead to multiple types of arrhythmia, nervous system injury, and abnormal changes in blood pressure. It can also increase the orthopedic perioperative risk in older patients, affect postoperative recovery, and even extend the length of hospital stay, and consequently, increase the economic burden. High-flow nasal cannula oxygen (HFNCO) is a new noninvasive oxygen therapy technology. As HFNCO can be used to improve oxygenation and manage hypoxemia rapidly and efficiently, it can heat and humidify inhaled air. Furthermore, it is convenient and comfortable\cite{2} and has been gradually used in clinics in recent years. Clinical reports suggest that it can be applied in the comprehensive treatment of various respiratory diseases, especially in the transitional treatment before extubation, prevention and treatment of respiratory failure after extubation, and treatment of postoperative patients complicated with hypoxemia\cite{3}. This randomized controlled trial aimed to report on the clinical efficacy of HFNCO and compare the effects of conventional mask oxygen and HFNCO on the recovery period of older (\geq 65 years) patients following orthopedic surgery. It was hypothesized that HFNCO may improve oxygen partial pressure and reduce the incidence of postoperative hypoxemia in older patients undergoing elective orthopedic surgery.
MATERIALS AND METHODS

Randomization and matching
From February to August 2021, 60 older patients eligible for orthopedic surgery under general endotracheal anesthesia at the Department of Orthopedics, Guangdong Hospital of Traditional Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangdong Province, China, were selected and randomly assigned to receive conventional mask oxygen or nasal high-flow oxygen inhalation, with 30 patients in each group. The envelope method was adopted for random grouping using random codes made in advance, with each code placed into the envelope and independently sealed. After the patients who met the inclusion criteria were enrolled into the study, the envelopes were opened in sequence, and the patients were treated as directed by the random-assignment card (Figure 1).

Participants
Patients undergoing orthopedic surgery, who met the surgical requirements as assessed by an orthopedic clinician, were considered for inclusion in this trial. The inclusion criteria were orthopedic patients aged ≥ 65 years who were selected for endotracheal general anesthesia, with American Society of Anesthesiologists (ASA) grade I-III, and provided written informed consent after being oriented about the study. The exclusion criteria were severe bullae of the lung, severe or extremely severe lung function, grade IV cardiac function grading, with known mental illness and/or inability to communicate with language partners, and/or serious non-cooperation.

Measurements
Electrocardiography, blood pressure, and SpO₂ were routinely monitored in all older patients undergoing orthopedic surgery after entering the operating room, and radial artery catheterization was performed to establish arterial pressure monitoring. Induction and maintenance of anesthesia were performed as follows: (1) Induction: Sufentanil, 0.3-0.4 μg/kg; etomidate, 0.3 mg/kg; cis-atracurium, 0.1-0.15 mg/kg; and (2) maintenance: Sevoflurane, 1%-2%; intermittent addition of sufentanil and cis-atracurium. After endotracheal intubation or laryngeal mask placement, the anesthesia machine was connected to control the respiration. The tidal volume and respiratory rate were 6-8 mL/kg and 12-15 times/min, respectively, and the end-expiratory carbon dioxide was maintained at 35-45 mmHg. In the event of blood pressure fluctuations during anesthesia, the clinical team determined the cause, including anesthesia, operation, or patient-related factors. For example, in a case of systolic blood pressure fluctuation, the clinical team decided to use drugs to control the patient’s blood pressure; then, the patient was transferred to the postanesthesia care unit (PACU) for extubation after surgery. After extubation, patients were randomly assigned to one of two groups to receive either conventional mask or HFNCO therapy. Blood gas analysis, including evaluation of the arterial partial pressure of oxygen (PaO₂), arterial partial pressure of carbon dioxide (PaCO₂) and pH before induction of anesthesia, during extubation, and 1 h after extubation, was conducted for all older orthopedic patients. Additionally, the heart rate (HR), blood pressure, and SpO₂ of all participants were observed before anesthesia induction, during extubation, and 10 min, 15 min, 30 min, and 1 h after extubation in older orthopedic patients. The patients’ oxygen tolerance scores were recorded as follows: (1) The patient was satisfied with the treatment; (2) the patient was not satisfied with the treatment; (3) the patient desired to remove the oxygen inhalation device but did not remove it by himself; (4) the patient removed the oxygen device by himself/herself; and (5) the patient refused to apply oxygen. Airway humidification was evaluated and was graded as satisfactory when the patient coughed up sputum easily, the sputum was thin, and the breathing was unobstructed. Conversely, humidification was unsatisfactory when the patient’s sputum was sticky and hard to cough up and the patient had a rapid HR and decreased peripheral blood oxygen saturation. Additionally, the incidence of complications 3 d after the operation were evaluated.

Interventions
The conventional mask group was treated with conventional mask oxygen inhalation for 1 h after extubation, with a flow rate of 2 L air plus 2 L O₂/min. Whereas, after extubation, the HNFCO group was treated with oxygen therapy using a high-flow nasal humidifier for 1 h via a special breathing line and nasal plug catheter. The gas flow rate was 40 L/min, the temperature was raised to 34 °C, and the inhaled oxygen concentration was 60%. If patients developed intolerance to HNFCO during treatment, the course of action was to immediately discontinue treatment and switch to conventional mask therapy to ensure safety and comfort.

Statistical analysis
The patient information database was created using Excel and SPSS 18.0 software packages. Continuous variables were described as median (interquartile range), while categorical variables were described as composition ratio and rate. For continuous variables with a normal distribution and homogeneity of variance, the independent t-test was used for inter-group comparison. The Mann-Whitney U test was used for continuous variables with non-normal distributions or uneven variance, and the paired t test...
(or Wilcoxon test) was used for intra-group comparison. When baseline values were unequal, univariate analysis of variance was performed. Between-group comparisons of categorical variables were performed using tests (or Fisher’s exact test). The rank sum test was used for comparison of grade data between groups. Significance level was set at $\alpha = 0.05$ (normality test $\alpha = 0.10$).

**RESULTS**

The preoperative baseline characteristics of the patients are presented in Table 1. There were no significant differences between the two groups in terms of sex, age, body weight, body mass index (BMI), and ASA grade ($P > 0.05$). There were no significant differences in the HR, mean arterial pressure (MAP), pH, $\text{paCO}_2$, $\text{paO}_2$, glucose level, and lactic acid level between the two groups before anesthesia and extubation. $\text{SpO}_2$ was not significantly different from that before anesthesia, but was at extubation ($P > 0.05$, Table 2).

Upon comparison of the outcome indexes after extubation between the two groups, the HFNCO group had significantly higher $\text{paO}_2$ than the conventional mask group 1 h after extubation ($P < 0.001$). There was no significant difference in $\text{paCO}_2$ between the two groups ($P > 0.05$). At extubation and 5 min, 15 min, and 30 min after extubation, the HFNCO group had significantly higher $\text{SpO}_2$ than the conventional mask group ($P < 0.05$). At extubation and at 5 min, 15 min, 30 min, and 1 h after extubation, the $\text{SpO}_2$ level of the HFNCO group was significantly higher than that of the conventional mask group. However, since there was a difference between the two groups before the intervention, i.e., at the time of extubation, we used the $\text{SpO}_2$ level at the time of extubation as a covariate for covariance analysis, and the corrected results showed no statistically significant differences between the two groups. Additionally, there were no significant differences in HR, MAP, PH, glucose level, and lactic acid level between the two groups ($P > 0.05$, Table 3).

The $\text{paCO}_2$ level of patients in the two groups was significantly higher at extubation and 1 h after extubation than before anesthesia ($P < 0.001$). The $\text{paCO}_2$ level was significantly lower at 1 h after extubation than at extubation ($P < 0.05$). There was no significant difference in the $\text{paO}_2$ level between the two groups before anesthesia and before extubation ($P > 0.05$). Both groups had significantly increased $\text{paO}_2$ 1 h after extubation compared with before anesthesia and at extubation ($P < 0.001$). The glucose level in both groups increased significantly 1 h after extubation compared with that before anesthesia and extubation ($P < 0.001$). In both groups, the lactic acid level was significantly increased at extubation compared with before anesthesia ($P < 0.001$) and significantly decreased at 1 h after extubation when compared with at extubation ($P < 0.001$).

Comparison of clinical efficacy indicators and complications between the two groups showed no significant differences in the oxygen tolerance score before PACU and pulmonary complications 3 d after surgery, based on airway humidification assessment ($P > 0.05$, Table 4).

**DISCUSSION**

Despite the development of new orthopedic surgery methods, age-related changes in lung physiology,
such as the deterioration of respiratory compliance and reduced responses to hypoxemia and other protective airway reflexes, increase the incidence of hypoxemia and pulmonary complications following orthopedic surgery in older patients[4]. Studies have shown that nearly 100% of patients will have atelectasis during general anesthesia, and postoperative hypoxemia and pulmonary complications may occur[5]. To some extent, this increases the perioperative risk of older orthopedic patients, affects postoperative recovery, and even extends the hospital stay, thus increasing the economic burden on patients[6]. HFNCO was originally used as a non-invasive, easy-to-use respiratory support therapy for acute hypoxic respiratory failure in adults, and it has been proven to be effective in patients with acute respiratory failure[5,7]. In recent years, high-flow oxygen therapy has been widely used in different clinical settings; however, experience in the use of HFNCO during the recovery period in older patients following orthopedic surgery under general anesthesia is limited, which prompted us to conduct this study.

This study showed that among older patients undergoing elective orthopedic surgery, the \( \text{paO}_2 \) in patients who used HFNCO was significantly higher than that in patients who used conventional mask. Additionally, \( \text{paO}_2 \) increased significantly at 1 h after extubation compared with that before anesthesia and at extubation. HFNCO provides a flow rate of up to 60 L/min, with almost no entrainment of room air during inhalation; this is combined with exhaled air from the upper respiratory tract. These mechanisms ensure a more reliable high-oxygen concentration. Flushing of the dead airway cavity by a trans-nasal high-flow oxygen humidifier also improves ventilation efficiency, reduces respiratory work, and produces positive end-expiratory pressure (PEEP), which may counteract intrinsic PEEP, improve oxygenation, and provide back pressure to enhance airway patency at expiration, thereby achieving more complete lung emptying[8,9]. These findings suggest that HFNCO may be more beneficial for older patients undergoing elective orthopedic surgery after intubation. After extubation, the \( \text{SpO}_2 \) level of the HFNCO group was significantly higher than that of the conventional mask group in covariance analysis, and the results showed no significant differences between the two groups after correction. Clinically, \( \text{SpO}_2 \leq 90\% \) was defined as hypoxemia; the \( \text{SpO}_2 \) level was > 90% in both the conventional mask and HFNCO groups at 15 min and 30 min after extubation. Although there was a significant difference, there was no specific clinical significance. Additionally, the inhaled oxygen concentration in the HFNCO group was the same as that in the mask group, but the HFNCO group had a higher oxygen flow; thus, better oxygen uptake could be achieved (higher arterial \( \text{paO}_2 \)). However, owing to the suctioning of air before anesthesia and extubation, the inhaled oxygen concentration was only 21%. Mechanical ventilation during surgery and anesthesia may cause lung injury. Additionally, there was a certain amount of oxygen reserve during extubation. In this study, four patients in the two groups had \( \text{paO}_2 \) lower than 80 mmHg after 1 h of treatment with different oxygen administration methods. All four patients were in the conventional mask group, indicating that there were no patients with hypoxemia in the HFNCO group. Therefore, HFNCO may significantly reduce the incidence of hypoxemia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Conventional mask group (n = 30)</th>
<th>HFNCO group (n = 30)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>72.8 ± 5.7</td>
<td>72.5 ± 4.3</td>
<td>0.778</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (30)</td>
<td>10 (33.3)</td>
<td>0.781</td>
</tr>
<tr>
<td>Female</td>
<td>21 (70)</td>
<td>20 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.4 ± 10.5</td>
<td>63.1 ± 8.0</td>
<td>0.756</td>
</tr>
<tr>
<td>BMI</td>
<td>25.1 ± 3.8</td>
<td>25.3 ± 3.5</td>
<td>0.793</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>15 (50)</td>
<td>21 (70)</td>
<td>0.114</td>
</tr>
<tr>
<td>III</td>
<td>15 (50)</td>
<td>9 (30)</td>
<td></td>
</tr>
<tr>
<td>Operation type</td>
<td></td>
<td></td>
<td>0.320</td>
</tr>
<tr>
<td>TKA</td>
<td>18 (60)</td>
<td>13 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Spinal surgery</td>
<td>6 (20)</td>
<td>11 (36.7)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>6 (20)</td>
<td>6 (20)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or n (%). ASA: American Society of Anesthesiologists; BMI: Body mass index; HFNCO: High-flow nasal cannula oxygen; TKA: Total knee arthroplasty.
Table 2 Comparison between the conventional mask group and the high-flow nasal cannula oxygen group before the intervention

<table>
<thead>
<tr>
<th></th>
<th>Conventional mask group (n = 30)</th>
<th>HFNCO group (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before anesthesia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>75.9 ± 11.4</td>
<td>74.7 ± 9.6</td>
<td>0.652</td>
</tr>
<tr>
<td>MAP</td>
<td>118.8 (109.0, 128.3)</td>
<td>119.8 (105.0, 126.6)</td>
<td>0.652</td>
</tr>
<tr>
<td>SpO₂</td>
<td>98.0 (97.0, 100.0)</td>
<td>99.0 (97.0, 100.0)</td>
<td>0.321</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 (7.40, 7.45)</td>
<td>7.42 (7.41, 7.44)</td>
<td>0.261</td>
</tr>
<tr>
<td>paCO₂</td>
<td>37.7 (75.4, 39.7)</td>
<td>38.9 (36.5, 40.6)</td>
<td>0.329</td>
</tr>
<tr>
<td>paO₂</td>
<td>78.9 (70.5, 85.3)</td>
<td>76.8 (70.0, 84.0)</td>
<td>0.953</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.5 (5.3, 6.6)</td>
<td>5.6 (5.3, 6.3)</td>
<td>0.947</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>1.3 (1.0, 1.8)</td>
<td>1.3 (1.1, 1.5)</td>
<td>0.689</td>
</tr>
<tr>
<td><strong>Extubation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>78.6 ± 11.8</td>
<td>73.9 ± 11.3</td>
<td>0.122</td>
</tr>
<tr>
<td>MAP</td>
<td>107.8 (102.3, 126.0)</td>
<td>110.5 (96.8, 117.5)</td>
<td>0.663</td>
</tr>
<tr>
<td>SpO₂</td>
<td>100.0 (99.0, 100.0)</td>
<td>100.0 (100.0, 100.0)</td>
<td>0.040</td>
</tr>
<tr>
<td>pH</td>
<td>7.33 (7.30, 7.35)</td>
<td>7.33 (7.30, 7.37)</td>
<td>0.367</td>
</tr>
<tr>
<td>paCO₂</td>
<td>48.1 (43.6, 54.1)</td>
<td>48.0 (43.6, 54.7)</td>
<td>0.976</td>
</tr>
<tr>
<td>paO₂</td>
<td>75.1 (64.0, 86.3)</td>
<td>74.0 (67.2, 89.7)</td>
<td>0.751</td>
</tr>
<tr>
<td>Glucose</td>
<td>6.2 (5.7, 7.5)</td>
<td>6.6 (5.4, 7.5)</td>
<td>0.907</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>1.8 (1.5, 2.2)</td>
<td>1.7 (1.3, 2.5)</td>
<td>0.941</td>
</tr>
</tbody>
</table>

1Mann-Whitney U test.

Data are presented as mean ± SD and median (interquartile spacing). HFNCO: High-flow nasal cannula oxygen; HR: Heart rate; MAP: Mean arterial pressure; paCO₂: Arterial partial pressure of carbon dioxide; paO₂: Arterial partial pressure of oxygen; SpO₂: Saturation of peripheral oxygen.

In the HFNCO group, paCO₂ increased from that before anesthesia to after extubation and decreased after 1 h of high-flow oxygen treatment. In the conventional mask group, paCO₂ increased from that before anesthesia to after extubation and decreased after 1 h of high-flow oxygen treatment. However, there was no significant difference in paCO₂ between the two groups at different time points, and the paCO₂ level was significantly lower at 1 h after extubation than before extubation. The patient may experience some lung injury during mechanical ventilation and surgery during anesthesia; thus, the paCO₂ level was slightly higher at extubation than before. However, after oxygen treatment for 1 h after extubation, the paCO₂ level was significantly lower than before indicating that adequate oxygen treatment after extubation may be conducive to the recovery of lung function.

The glucose levels in both groups at 1 h after extubation were significantly higher than those before anesthesia and at extubation. This was thought to be mainly related to surgical stress. Hyperglycemia in perioperative patients has been identified as a risk factor for a poor prognosis after various surgical procedures[10]. In this study, some patients had diabetes, suggesting that perioperative blood glucose control is also crucial. The lactic acid levels increased from 1.4 to 1.9 mmol/L and then decreased to 1.5 mmol/L in both groups. Although there was a significant difference, both were within the normal ranges and had no clinical significance. Perioperative adverse events can affect the prognosis of patients, especially during and after surgery, and possible anesthesia-related adverse events are often ignored. Intraoperative visceral tissue perfusion can easily be damaged. As a good indicator of tissue perfusion, lactic acid should not be ignored during the perioperative period. Oxygen is carried by blood flow, mainly by hemoglobin, for microcirculation. Perioperative patients with reduced circulating blood volume (insufficient cardiac output), insufficient hemoglobin, or reduced hematocrit will experience reduced oxygen delivery, resulting in tissue hypoperfusion[11,12]. Hypoperfusion and the resulting tissue hypoxia are common causes of a poor prognosis. During operation, patients are in a controlled environment and have relatively stable oxygen inhalation. However, because of various subjective and objective factors after catheterization, it is important to ensure a certain amount of oxygen inhalation to enable tissue perfusion, which is also an advantage of HFNCO.

In cases of coronavirus disease (COVID-19), patients with severe illness often have varying degrees of hypoxia and dyspnea; therefore, respiratory support is very important for these patients. Studies have
shown that compared with conventional oxygen therapy[13], early HFNCO oxygen therapy can improve the oxygenation function and respiratory rate of patients with severe COVID-19, while improving the patient’s infection indicators and reducing the length of stay in the intensive care unit. Consistent with our study, Oczkowski et al[14] showed that HFNCO would lead to a higher $paO_2/\text{FiO}_2$ ratio and $paO_2$ value, but has no significant effect on $paCO_2$ value. In patients with no COVID-19, the European Respiratory Society recommends HFNCO instead of conventional nasal intubation and noninvasive ventilation for patients with hypoxic respiratory failure[14].

Multiple studies have shown that HFNCO can potentially promote spontaneous breathing, prevent patient fatigue, and reduce the risk of self-induced lung injury. HFNCO can improve patient comfort and tolerance compared with conventional mask oxygen delivery[15]. The patients included in this study were evaluated under different types of HFNCO environmental comfort. Oxygen treatment 1 h after extubation, the airway of wetting effect basic satisfaction, and oxygen tolerance grade, which may result in oxygen treatment for a shorter duration. This was one of the limitations of this experiment. Additionally, the postoperative follow-up time interval was shorter, and fewer participants were assessed for comfort. Thus, this may only be regarded as a secondary psychological result; for example, when the patients' physical and psychological comfort requirements are satisfied, they will have a sense of relief. Overall, no postoperative complications were observed; this may be related to patients' subjective reporting or the short observation time, which is thus another study limitation. There was no statistically significant difference in airway humidification between the two groups in our study. However, Wang et al[16] showed in their study that the application of HFNCO in senior patients with LRTI could improve respiratory humidification, reduce the number of sputum aspirations, and improve anti-inflammatory effects. This may be due to our short observation period and the relatively simple method for evaluating airway humidification.

### Table 3: Comparison between the conventional mask group and the high-flow nasal cannula oxygen group after the intervention

<table>
<thead>
<tr>
<th></th>
<th>Conventional mask group (n = 30)</th>
<th>HFNCO group (n = 30)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5 min after extubation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>76.0 ± 12.8</td>
<td>71.3 ± 11.0</td>
<td>0.138</td>
</tr>
<tr>
<td>MAP</td>
<td>108.3 (99.0, 120.5)</td>
<td>105.5 (96.3, 115.1)</td>
<td>0.473</td>
</tr>
<tr>
<td>$SpO_2$</td>
<td>100.0 (97.8, 100.0)</td>
<td>100.0 (100.0, 100.0)</td>
<td>0.032</td>
</tr>
<tr>
<td><strong>15 min after extubation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>76.6 ± 12.7</td>
<td>71.4 ± 10.5</td>
<td>0.091</td>
</tr>
<tr>
<td>MAP</td>
<td>108.5 (96.0, 121.9)</td>
<td>105.3 (95.9, 118.6)</td>
<td>0.620</td>
</tr>
<tr>
<td>$SpO_2$</td>
<td>100.0 (98.0, 100.0)</td>
<td>100.0 (100.0, 100.0)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>30 min after extubation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>75.9 ± 13.1</td>
<td>70.3 ± 8.8</td>
<td>0.054</td>
</tr>
<tr>
<td>MAP</td>
<td>107.5 (97.0, 117.6)</td>
<td>111.0 (100.3, 117.8)</td>
<td>0.673</td>
</tr>
<tr>
<td>$SpO_2$</td>
<td>100.0 (98.8, 100.0)</td>
<td>100.0 (100.0, 100.0)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>1 h after extubation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>76.5 ± 13.6</td>
<td>71.0 ± 9.2</td>
<td>0.073</td>
</tr>
<tr>
<td>MAP</td>
<td>105.8 (97.3, 119.1)</td>
<td>107.5 (110.5, 121.0)</td>
<td>0.647</td>
</tr>
<tr>
<td>$SpO_2$</td>
<td>100.0 (99.0, 100.0)</td>
<td>100.0 (100.0, 100.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 (7.34, 7.38)</td>
<td>7.36 (7.33, 7.37)</td>
<td>0.652</td>
</tr>
<tr>
<td>$paCO_2$</td>
<td>44.0 (40.1, 48.2)</td>
<td>45.3 (41.8, 49.8)</td>
<td>0.761</td>
</tr>
<tr>
<td>$paO_2$</td>
<td>114.0 (83.5, 147.6)</td>
<td>194.9 (162.9, 242.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Glucose</td>
<td>8.3 (6.5, 8.9)</td>
<td>7.6 (6.5, 8.7)</td>
<td>0.569</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>1.4 (1.1, 1.7)</td>
<td>1.4 (1.1, 1.8)</td>
<td>0.941</td>
</tr>
</tbody>
</table>

1Mann-Whitney U test.

Data are presented as mean ± SD and median (interquartile spacing). HFNCO: High-flow nasal cannula oxygen; HR: Heart rate; MAP: Mean arterial pressure; $paCO_2$: Arterial partial pressure of carbon dioxide; $paO_2$: Arterial partial pressure of oxygen; $SpO_2$: Saturation of peripheral oxygen.
CONCLUSION

This study found that HFNCO could effectively improve oxygen partial pressure and respiratory function in older patients undergoing elective orthopedic surgery. Thus, HFNCO can be used to prevent postoperative hypoxemia.

ARTICLE HIGHLIGHTS

Research background
In the future, we can extend the follow-up time, refine the evaluation indicators, further clarify the postoperative complications of elderly orthopedic surgery patients and use traditional Chinese medicine for intervention.

Research motivation
High-flow nasal cannula oxygen (HFNCO) can improve oxygen partial pressure and respiratory function in elderly patients undergoing orthopedic surgery under general endotracheal anesthesia. Thus, HFNCO can be used to prevent postoperative hypoxemia.

Research objectives
In comparison between the two groups, arterial partial pressure of oxygen (PaO\textsubscript{2}) in HFNCO group was significantly better than that in the conventional group, while no significant differences were observed in other indicators. In intra-group comparison, PaO\textsubscript{2} had statistical differences at all time periods, pressure of carbon dioxide (PaCO\textsubscript{2}) had statistically significant differences before and after extubation, and the other data showed no significant differences.

Research methods
In this prospective randomized controlled trial, 60 older patients who underwent orthopedic surgery under general anesthesia were randomly divided into two groups: those who used conventional face mask and those who used HFNCO. Blood gas analysis, including evaluation of the PaO\textsubscript{2}, PaCO\textsubscript{2} and pH before induction of anesthesia, during extubation, and 1 h after extubation, was conducted for all older orthopedic patients. The patient information database was created and analysis using Excel and SPSS 18.0 software packages.

Research results
This randomized controlled trial aimed to report on the clinical efficacy of HFNCO and compare the effects of conventional mask oxygen and HFNCO on the recovery period of older (≥ 65 years) patients following orthopedic surgery.

Table 4 Postoperative evaluation of the patients in the conventional mask group and high-flow nasal cannula oxygen group

<table>
<thead>
<tr>
<th>Patients’ oxygen tolerance score</th>
<th>Conventional mask group (n = 30), n (%)</th>
<th>HFNCO group (n = 30), n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29 (96.7)</td>
<td>30 (100)</td>
<td>0.078¹</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (3.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Airway humidification evaluation: “yes” indicates satisfactory airway humidification; “no” indicates unsatisfactory airway humidification. Data are presented as n (%). HFNCO: High-flow nasal cannula oxygen.

¹Fisher’s exact test.
Research conclusions
As HFNCO can be used to improve oxygenation and manage hypoxemia rapidly and efficiently, it can heat and humidify inhaled air. Furthermore, it is convenient and comfortable and has been gradually used in clinics in recent years.

Research perspectives
Hypoxemia may cause postoperative delirium and wound infection, and in severe cases, it may lead to multiple types of arrhythmia, nervous system injury, and abnormal changes in blood pressure. It can also increase the orthopedic perioperative risk in older patients, affect postoperative recovery, and even extend the length of hospital stay, and consequently, increase the economic burden. We hypothesized that HFNCO has an advantage over conventional mask oxygen in the resuscitation period of older orthopedic patients.

FOOTNOTES
Author contributions: Li XN was the main contributor to this work; Li XN, Zhou CC, Jia B, Li XY, Zhao GF, and Ye F designed the research; Li XN and Ye F performed the research; Lin ZQ, Li XY contributed the new analytic tools; Li XN and Zhou CC analyzed the data; Li XN and Ye F wrote the paper.

Institutional review board statement: The study was reviewed and approved by the Institutional Ethics Committee of the Ethics Committee of Guangdong Hospital of Conventional Chinese Medicine on January 29, 2021, No. YF2021-014-01.

Clinical trial registration statement: This study is registered at Clinical hospital center “Chinese Clinical Trial Registry” trial registry, No. ChiCTR2100044463.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at yepainclinic@163.com.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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REFERENCES


Assessment tools for differential diagnosis of neglect: Focusing on egocentric neglect and allocentric neglect

Sang-Hyeok Lee, Byeong-Chan Lim, Chan-Young Jeong, Jun-Hyeok Kim, Woo-Hyuk Jang

Abstract

BACKGROUND
There are very few studies on the differential diagnosis between egocentric neglect (EN) and allocentric neglect (AN).

AIM
To investigate the overall trend of the previously developed assessment tools by conducting a descriptive review of the studies on assessment tools that can perform a differential diagnosis of EN and AN.

METHODS
The data were collected by using databases such as Google Scholar, PubMed, and ScienceDirect. The most commonly used search terms were “neglect”, “stroke”, “egocentric neglect”, and “allocentric neglect”.

RESULTS
A total of seven studies that met the inclusion criteria were selected and analyzed. We were able to confirm the research process, test method, and differential diagnosis criteria of the seven presented assessment tools from four studies on paper-based tests and three studies on computerized tests. The majority of the tests were carried out via the cancellation method using stimuli such as everyday objects or numbers. EN distinguished the left from right based on the test paper, while AN distinguished the left from right based on stimuli. In order to perform differential diagnosis, the difference in the number of left and right responses or non-responses was used based on the EN and AN criteria.

CONCLUSION
It was confirmed that all the seven assessment tools can effectively perform differential diagnosis of EN and AN. This study may provide important data that can be used in clinical practice for differential diagnosis and future intervention planning for neglect patients.
INTRODUCTION

Neglect is a neurological deficit due to brain damage resulting in difficulty identifying information input from the opposite direction\(^1\,\,2\). It is the most frequent serious sequela following right hemisphere damage\(^3\). The main symptom of brain damage is difficulty in recognizing objects or people in the opposite space despite having adequate sensorimotor ability\(^4\). These symptoms make it difficult for a person to use their eyes, arms, and legs to search within a neglected space\(^5\). They also require assistance for independent daily life due to risk of secondary accidents including falls\(^6\). Neglect is classified into sensory neglect and motor neglect based on deficit type, and personal neglect, peripersonal neglect, and extra-personal neglect based on the distance of occurrence\(^7\). Due to various symptoms, neglect causes delays in rehabilitation treatment and recovery\(^8\).

In 2001, Ota et al\(^9\) conducted a study for the development of an assessment tool that can differentiate between two new types of neglect symptoms. The first type of neglect is egocentric neglect (EN), which focuses on an individual and neglects information in the opposite side of the brain damage. The second type of neglect is allocentric neglect (AN), which neglects information in the opposite side of the brain damage, regardless of the object’s location\(^9\,\,10\). EN is also known as viewer-centered neglect, whereas AN is known as stimulus-centered neglect\(^11\). The research of Ota et al\(^9\) led to the development of the apples test and the broken hearts test for better differentiation of the two types of neglect\(^12\,\,13\).

A study that measured language, memory, number, praxis, extinction, and controlled attention confirmed the difference between EN and AN symptoms. EN patients showed a lower performance in the memory domain, while AN patients showed a lower performance in all other domains\(^12\). AN also has a more adverse effect on daily life performance than EN\(^14\), and AN patients recover at a slower and more difficult rate than that of the EN patients\(^15\). A new treatment method is deemed necessary as the existing neglect treatment has no effect on AN\(^16\).

Differentiation is important for accurate diagnosis and confirmation of various symptoms in patients with neglect. This is essential for establishing an effective intervention\(^7\,\,17\). Studies have been conducted to systematically review treatments, effects, and assessment tools for neglect\(^5\,\,18-22\), but none have examined the assessment tools that can effectively differentiate between EN and AN.

The purpose of this study was to review the assessment tools that can differentiate between EN and AN, and investigate the overall trend of the Ota test and newly developed assessment tools by analyzing various studies.

MATERIALS AND METHODS

Data based on the articles on assessment tools that can differentiate between EN and AN were collected for this study by using databases such as Google Scholar, PubMed, and ScienceDirect. The search keywords used were “neglect”, “stroke”, “egocentric neglect”, “allocentric neglect”, “viewer-centered neglect”, “stimulus-centered neglect”, “test”, “evaluation”, and “assessment”. The article search yielded 290 articles, among which seven were selected, excluding duplicated studies that met the exclusion criteria (Figure 1 and Table 1). In addition, we conducted a relevant search by Reference Citation Analysis (https://www.referencecitationanalysis.com/) and cited high-quality references.
Table 1 Analysis of studies about assessment tools to distinguish between egocentric neglect and allocentric neglect

<table>
<thead>
<tr>
<th>Name of assessment</th>
<th>Ref.</th>
<th>Type of participants</th>
<th>Type of assessment</th>
<th>Cut-off score</th>
<th>Time limit</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ota test</td>
<td>Ota et al[9], 2001</td>
<td>n = 2. Stroke patients (only RBD)</td>
<td>Pencil and paper</td>
<td>EN: The number of omitted complete targets; AN: The number of selected incomplete targets</td>
<td>No limit</td>
<td>The test is developed in order to distinguish EN and AN with one task</td>
</tr>
<tr>
<td>Apples test</td>
<td>Bickerton et al[2], 2011</td>
<td>n = 111. Experimental group: 25 (stroke patients-LBD: 7, RBD: 18); Control group: 86 (healthy participants)</td>
<td>Pencil and paper</td>
<td>Left EN: &gt; 2; Right EN: &lt; -2; Left AN: &gt; 1; Right AN: &lt; -1</td>
<td>5 min</td>
<td>The test provides a clinically applicable measure of different forms of neglect (EN and AN)</td>
</tr>
<tr>
<td>Broken hearts test</td>
<td>Demeyere et al[13], 2015</td>
<td>n = 348. Experimental group: 208 (acute stroke patients-LBD: 84, RBD: 101, Both: 19, Unknown: 4); Control group: 140 (healthy participants)</td>
<td>Pencil and paper</td>
<td>Left EN: &gt; 3; Right EN: &lt; -3; Left AN: &gt; 1; Right AN: &lt; -1</td>
<td>3 min</td>
<td>The test presented the validity and applicability of the OCS in acute stroke assessment</td>
</tr>
<tr>
<td>Computerised cancellation test</td>
<td>Mizuno et al [24], 2015</td>
<td>n = 19. Experimental group: 3 (stroke patients-only RBD, AND has neglect: 2, AND without neglect: 1); Control group: 16 (healthy participants)</td>
<td>Digital test (touchscreen)</td>
<td>EN: The number of omitted complete targets; AN: The number of selected incomplete targets (Ota test only)</td>
<td>No mention</td>
<td>The test is developed a computer-based programme to evaluate EN and AN</td>
</tr>
<tr>
<td>MonAmour robot test</td>
<td>Montedoro et al[25], 2019</td>
<td>n = 91. Experimental group: 35 (stroke patients-LBD: 12, RBD: 23, AND has EN: 25, AND without EN: 10; Control group: 56 (healthy participants)</td>
<td>Digital test (Robot)</td>
<td>Left EN: ≥ 1Right EN: ≤ -1Left AN: ≥ 1Right AN: ≤ -1</td>
<td>7 s (each trial)</td>
<td>The test is a valid, sensitive, and reliable tool that can diagnose EN and AN</td>
</tr>
<tr>
<td>3s spreadsheet test v2</td>
<td>Chen et al [23], 2021</td>
<td>n = 209. Experimental group: 23 (stroke patients, only RBD); Control group: 186 (healthy participants)</td>
<td>Pencil and paper test</td>
<td>Left EN: &gt; 3; Right EN: &lt; -3; Left AN: &gt; 3; Right AN: &lt; -3</td>
<td>No limit (mean ± SD): 202.0 ± 64.6 s</td>
<td>The test may increase the comprehensiveness of the neglect assessment</td>
</tr>
<tr>
<td>ReMoVES platform</td>
<td>Ferraro et al [20], 2021</td>
<td>n = 18. Experimental group: 12 (neglect patients); Control group: 6 (healthy participants)</td>
<td>Digital test (touchscreen)</td>
<td>Left EN: &gt; 2; Right EN: &lt; -2; Left AN: &gt; 1; Right AN: &lt; -1 (apples test only)</td>
<td>5 min (apples test only)</td>
<td>Traditional and digital versions are correlated and they yield very similar results, thus denoting them to be interchangeable</td>
</tr>
</tbody>
</table>

RBD: Right brain damaged; LBD: Left brain damaged; EN: Egocentric neglect; AN: Allocentric neglect.

RESULTS

Ota et al[9] conducted a study in order to develop the Ota test for the differential diagnosis of EN and AN in two stroke patients with neglect following right hemisphere damage. In the development process, the two sub-assessments performed were circle discriminative cancellation (CDC) task and triangle discriminative cancellation (TDC) task. All tests were performed on an A3 paper. For the CDC task, 60 stimuli consisting of complete circle forms (20 stimuli, complete targets) and incomplete circle forms (40 stimuli: 20 left incomplete, 20 right incomplete, incomplete targets) were randomly scattered and placed. TDC task is similar to CDC task, except that the stimuli are in the form of triangles (Figure 2A). This test, which had no time limit, required the subjects to draw a circle to represent complete stimuli and a line to represent incomplete stimuli. Each test began with the paper presented in an upright position, followed by a re-test in which the paper was presented upside down. One test consisted of four trials (two CDC tasks and two TDC tasks). Results were obtained from all subjects who performed the second test similarly on a different day. The diagnostic methods suggested in this study are as follows. First, EN diagnosis was presented as an omission error by removing a circle in the complete stimuli on the left side of the test paper. Next, AN diagnosis was presented as an inclusion error by adding a line to the incomplete stimuli. The test may increase the comprehensiveness of the neglect assessment by showing that subject 1 was EN and subject 2 was AN[9]. The limitations of this study are as follows. First, generalization may be difficult due to the small number of study participants. Second, the date interval between the tests and the reason for the four trials in this study were not clearly stated. Third, the severity of neglect cannot be examined because of the missing cut-off score. Therefore, it can only be used to distinguish EN from AN. Lastly, since there were two patients with left neglect, the study only showed the left-centered diagnostic methods for EN and AN. However, the diagnostic method for right neglect was not described.
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DOI: 10.1299/wjcc.v10.i24.8625  Copyright ©The Author(s) 2022.

Figure 1 Flow diagram for identifying assessment tools for egocentric and allocentric neglect.

Figure 2 Test sheet and sort of targets. A: Ota test; B: Apples test; C: MonAmour robot test; D: 3s spreadsheet test v2. Red arrows indicate complete targets, green arrows indicate left incomplete targets, and yellow arrows indicate right incomplete targets. CDC: Circle discriminative cancellation; TDC: Triangle discriminative cancellation.

Bickerton et al.[12] compared the apples test, which can perform a differential diagnosis of EN and AN, with the star cancellation test, a standardized neglect assessment tool, in a validation study involving an experimental group (25 stroke patients) and a control group (86 normal subjects). All tests were conducted on an A4 paper, and 150 stimuli consisting of complete apple-shaped stimuli (50 stimuli, complete targets) and incomplete apple-shaped stimuli (100 stimuli: 50 left incomplete, 50 right incomplete, incomplete targets) were randomly scattered (Figure 2B). The test paper was divided into 10
invisible cells (5 columns and 2 rows). Each cell received 15 apple-shaped stimuli (3 large apples and 12 small apples), including complete apple-shaped stimuli and left or right incomplete apple-shaped stimuli. The subjects were specifically instructed to mark only the complete apple shape, regardless of size. The test, which had a time limit of 5 min, was performed with a simple preliminary test (up to 2 times) to familiarize the subjects with the test method. The diagnostic methods and cut-off scores proposed in the study are as follows. First, EN is diagnosed by comparing the correct answers in the left and right columns of the test paper. If the value obtained by subtracting the number of complete apple-shaped stimuli in the left cells from the selected number of complete apple-shaped stimuli in the right cells exceeds 2, it is presented as left side EN, and if it is less than -2, it is presented as right side EN. However, the middle 2 out of 10 cells were not used for scoring. Second, the difference in false positive responses based on the stimuli is used to diagnose AN. If the value obtained by subtracting the number of selected right incomplete apple-shaped stimuli (right incomplete targets) from the number of selected left incomplete apple-shaped stimuli (left incomplete targets) exceeds 1, it is presented as left side AN, and if it is less than -1, it is presented as right side AN. According to the study result, five subjects of the experimental group had EN, two had AN, and five had both EN and AN, thereby suggesting the possibility of differentiation. The apples test was found to be as sensitive and highly validated as the star cancellation test [12]. However, this study had limitations. First, the study had a relatively small number of subjects. Second, the preliminary test did not mention the practice paper. Third, a time limit was set for the test, but it was not used in the differential diagnosis process. Lastly, exact figures were not presented during the apples test validity verification process.

Demeyere et al. [13] conducted a study involving an experimental group (208 stroke patients) and a control group (146 normal subjects) in order to develop the Oxford cognitive screen (OCS) to effectively measure cognitive function. The broken hearts test is a sub-test of OCS that can distinguish between EN and AN. During the development process, the sensitivity of the broken hearts test was compared to that of the star cancellation test, a standardized neglect evaluation tool. All tests were conducted on an A4 paper, and 150 stimuli consisting of complete heart-shaped stimuli (50 stimuli, complete targets) and incomplete heart-shaped stimuli (100 stimuli: 50 left incomplete, 50 right incomplete, incomplete targets) were randomly scattered and placed. In the test methods, the subjects were instructed to strike through the complete heart-shaped stimuli, regardless of heart size. The test, which had a time limit of 3 min, was performed after test method familiarization via a simple preliminary test. The diagnostic methods and cut-off scores proposed in the study are as follows. First, EN is compared by comparing the correct answers in the test paper’s left and right columns. If the value obtained by subtracting the number of complete heart-shaped stimuli in the left cells from the selected number of complete heart-shaped stimuli in the right cells exceeds 3, it is presented as left side EN, and if it is less than -3, it is presented as right side EN. However, the middle two out of ten cells were not used for scoring. Next, the difference in false positive responses based on the stimuli is used to diagnose AN. If the value obtained by subtracting the number of selected right incomplete heart-shaped stimuli (right incomplete targets) from the number of selected left incomplete heart-shaped stimuli (left incomplete targets) exceeds 1, it is presented as left side AN, and if it is less than -1, it is presented as right side AN. Based on the study result, 25% of the experimental group had EN, 11.9% had AN, and 13.6% had both EN and AN. The broken hearts test validation result was also very high at 94.12% [13]. Although a test time limit was set, it was not used in the differential diagnosis process.

Mizuno et al. [24] conducted a study involving an experimental group (3 stroke patients, but only 2 had symptoms of neglect) and a control group (16 normal subjects) to develop the computerised cancellation test (CCT) for the differential diagnosis of EN and AN. During the development process, the conventional behavioral inattention test (BIT-C), a standardized neglect evaluation tool, was also implemented to verify CCT sensitivity. CCT can perform digital tests of circle discriminative cancellation task (CDC task), simple cancellation test, visuomotor search test, and visual search test through a 32-inch touch screen called TouchUbiCom; however, only the CDC task was able to perform a differential diagnosis of EN and AN. The computerized CDC task test presented in CCT is similar to the paper-based CDC task test developed by Ota et al. [9]. The difference is that a person has to touch the complete targets on the screen with a finger, and the result is automatically calculated. According to the study result, subject 1 presented with EN in the experimental group, subject 2 with AN, and the remaining one subject without neglect did not present with either EN or AN. Furthermore, CCT was found to be as sensitive as BIT-C [24]. The limitations of this study are as follows. First, generalization may be difficult due to the small number of study participants. Second, neglect severity cannot be examined because there is no cut-off score; thus, it can only be used to distinguish EN from AN. Third, requiring a special touch screen for the test may increase the cost. Lastly, exact figures were not presented in the CCT sensitivity verification process.

Montedoro et al. [25] conducted a study involving an experimental group (35 stroke patients) and a control group (56 normal subjects) to develop the MonAmour robot test (MRT) for the differential diagnosis of EN and AN. During the development process, it was compared with the bells test, a standardized neglect evaluation tool, to verify MRT sensitivity. MRT used the REAplan® robot equipped with a test screen and a joystick (control handle). The screen is divided into 30 invisible cells (6 rows and 5 columns), and 120 stimuli were randomly placed, with four stimuli in each cell. The test employs human-shaped stimuli with raised hands (left, right, and both hands, targets) and four instrument-
shaped stimuli (distractors) (Figure 2C). In 29 out of 30 cells, four instrument-shaped stimuli are presented, and one human-shaped stimulus (left hand: 30 times, right hand: 30 times, both hands: 30 times, and catch trial: 10 times) and three instrument-shaped stimuli are rearranged. The test, which included 100 trials at 7-s intervals, required the subject to push the joystick forward when a person raising both hands appeared, and to pull the joystick back when a person with one hand (left hand, right hand) appeared. The test was performed after familiarization with the test methods through a simple preliminary test (up to 10 times). The diagnostic methods suggested in this study are as follows. First, EN is diagnosed by comparing the mean reaction time on the right area or the number of non-responses (omission error) when human-shaped stimuli (left, right, and both hands) are presented in the left and right columns based on the test screen. If the value obtained by subtracting the number of responses that missed the human-shaped stimuli in the right column from the number of responses that missed the human-shaped stimuli in the left column is 1 or greater, it was presented as left side EN, and if it was -1 or less, it was presented as right side EN. Meanwhile, AN is diagnosed when human-shaped stimuli (including stimuli with either the left or right hand raised) respond in the opposite direction to the instruction (false positive response). If the value obtained by subtracting the number of opposite reactions to the human-shaped stimuli with a right hand raised (left incomplete targets) from the number of opposite reactions to the human-shaped stimuli with a left hand raised (right incomplete targets) is 1 or greater, it is presented as left side AN, and if it is -1 or less, it is presented as right side AN. Based on the study result, 19 subjects of the experimental group had EN, two had AN, and eight had both EN and AN, thereby suggesting the possibility of differentiation. The verified MRT sensitivity was found to be 94% of the overall standard, confirming a high correlation with the bells test[25]. The study’s limitations include economic burden and space for installation due to the specialized high-priced robot required.

Chen et al[23] conducted a study involving an experimental group (23 stroke or neglect patients) and a control group (186 normal subjects) in order to develop the 3 s spreadsheet test v2 for the EN and AN differential diagnosis. The test was conducted on a letter size paper (8.5 × 11 in) with 140 cells (10 cells per row and 14 cells per column), in which the digit strings served as stimuli. The digit strings had a minimum of four digits and a maximum of nine digits, with digits 0 to 9 being listed repeatedly. The test, which had no time limit, required the subject to find the correct answer 3 (targets) in all digit strings in the cell and strike through (correct answers: 120, other distractors: 720). If the digit strings are an odd number, 3 was not placed in the middle number (Figure 2D). The diagnostic methods and cut-off scores suggested in the study are as follows. First, EN diagnosis was analyzed by the difference in omission errors based on the test paper. If the value obtained by subtracting the number of omissions of the correct stimuli in the left region from the number of omissions of the correct stimuli in the right region exceeded 3, it was presented as left side EN, and if it was less than -3, it was presented as right side EN. For AN diagnosis, the digit strings were divided in half based on the digit strings presented for each cell in the test. If the value obtained by subtracting the number of omissions of the correct stimuli in the right area from the number of omissions of the correct stimuli in the left area exceeded 5, it was presented as left side AN, and if it was less than -3, it was presented as right side AN. Based on the study result, three out of 23 subjects in the experimental group had EN, two had AN, and 18 had both EN and AN, thereby suggesting the possibility of differentiation[23]. The study’s limitation is that the subjects may experience high test fatigue due to the 840 stimuli, which is higher compared to the other tests.

Ferraro et al[26] investigated the possibility of replacing the pen and paper test with digital tests such as Albert’s test, line bisection test, and apples test built in the ReMoVES platform for an experimental group (12 neglected patients) and a control group (6 normal patients)[26]. The ReMoVES platform is a computerized test program developed by the University of Genova, and only the apples test was able to differentiate between EN and AN among the three built-in tests. The computerized apples test presented in the ReMoVES platform is similar to the paper-based apples test studied by Mancuso et al[27]. However, it requires touching the complete apple-shaped stimuli presented on the screen with a finger, and the result is automatically calculated. The study result showed that the paper-based test and computerized test produced similar results in the subject's test performance process, and they can be used interchangeably[26]. The limitations of this study are as follows. First, personal information (e.g., gender, age, and disease) was not presented for the 12 experimental groups. Finally, generalization is difficult due to the small number of study participants (Figure 2).

**DISCUSSION**

**Comprehensive analysis of the seven assessment tools for differential diagnosis**

AN has more adverse effects on cognitive function, activities of daily living, and rehabilitation speed than EN. It was also confirmed that the existing neglect treatment had no significant effect on AN patients. Therefore, seven assessment tools that can effectively differentially diagnose EN and AN were analyzed.

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**August 26, 2022 | Volume 10 | Issue 24 | WJCC**
First, the study results showed that cancellation test type tests were developed in the studies as the most common feature, and the test stimuli presented during the research process were commonly encountered shapes in everyday life, such as circles, triangles, apples, hearts, and numbers[9,12,13,23-26]. Furthermore, it has been confirmed that the stimuli presented in most studies were complete forms and left or right incomplete[9,12,13,24-26]. According to the diagnostic methods presented in this study, EN is mainly the difference in the number of correct answers in the left and right areas on the test paper or screen, and AN was presented as the difference in the number of incorrect answers on incomplete forms in the left and right areas based on stimuli (false positive response)[9,12,13,24,26]. This is thought to be presented for accurate differential diagnosis, taking into account the concept of EN neglecting information centered on the individual (self) and AN neglecting information centered on the object (stimuli). However, the MonAmour robot test studied by Montedoro et al.[25] showed both the EN and AN diagnostic methods presented as a difference in the number of incorrect answers (non-response, opposite response). In comparison with the other tests, it is considered to be the diagnostic method designed according to the test characteristics, in which the stimuli are newly rearranged for each trial, and must respond to both correct and incorrect answers. According to the study conducted by Chen et al [23] on ‘3s spreadsheet test v2’, both the EN and AN diagnostic methods were presented as the difference in the number of omission of correct answers (omission errors). In comparison with the other tests, it is considered to be the diagnostic method designed according to the test characteristics, in which the stimuli used are presented only as the correct stimuli (targets) and other stimuli (distractors). Furthermore, four articles reviewed the pencil and paper tests[9,12,13,23], and three articles reviewed the digital[24-26]. All of the seven presented assessment tools can effectively perform a differential diagnosis of EN and AN, and Ferraro et al[26] confirmed that the paper-based test and the digital test are interchangeable with each other.

The limitations of the studies are as follows. First, they are difficult to generalize due to the small number of study subjects[9,24,26]. Second, although the diagnostic criteria for EN and AN were presented, a cut-off score to evaluate the severity of neglect was not presented[9,24]. Third, accurate figures were not presented in the assessment tool verification process[12,24]. Fourth, the diagnostic criteria for EN and AN were only focused on the left side, so the diagnosis criteria for right neglect were not presented[9,24]. Fifth, although the time limit of the test was set, it was not used to determine the degree of neglect[12,13]. Lastly, there are issues in regard to space due to cost and installation location for the digital tests[24,25]. In future studies, the following is recommended to complement the limitations of the previous studies: (1) Conduct research with a sufficient number of subjects; (2) Provide a cut-off score required in order to confirm the severity of neglect; (3) Suggest the severity according to the type of neglect by using the time limit of the test; and (4) Consider economic and spatial problems caused by the equipment required for the digital tests.

CONCLUSION

In this study, we review the literature studying assessment tools for the differential diagnosis of EN and AN. Accordingly, seven tests (pencil and paper: 4 times, digital test: 3 times) were tested and effective, and differential diagnosis can be conducted when the difference in response to various stimuli is used.

In conclusion, these results might offer an easier differential diagnosis of AN, and appropriate intervention at an early stage of injury. In the case of a patient with both EN and AN, it might be possible to seamlessly modify the detailed direction of intervention by determining the improvement of neglect via continuous assessment. Finally, the data discussed in this work may provide guidance for developing more convenient and various differential diagnosis methods and new intervention methods for AN as diverse as those for EN.

ARTICLE HIGHLIGHTS

Research background
There are various types of neglect, and the symptoms are also diverse. However, review studies on the differential diagnosis of the relatively recently discovered allocentric neglect (AN) and the already known egocentric neglect (EN) are lacking.

Research motivation
Compared to EN, AN has a more adverse effect on daily life, and the recovery rate is lower. In addition, the conventional treatment for EN is not effective in the treatment of AN. Therefore, the distinction between AN and EN is very important.
Research objectives
By reviewing the studies on differential diagnosis, we tried to find out the overall trend of the newly developed evaluation tools.

Research methods
A literature search on differential diagnosis was conducted through a search according to appropriate keywords.

Research results
Seven relevant papers were collected (paper-and-pencil 4, digital 3).

Research conclusions
All tests were effective in the differential diagnosis of EN and AN.

Research perspectives
A more effective intervention will be possible through an accurate differential diagnosis. It is hoped that more treatments for AN will be developed in the future.

FOOTNOTES

Author contributions: Lee SH, Lim BC, Jeong CY, and Kim JH contributed to article investigation and collection, review, and writing; Jang WH contributed to conceptualization, editing, and supervision; and all authors have read and agreed to the published version of the manuscript.

Supported by the National Research Foundation of Korea Grant funded by the Korea government, No. 2021R1G1A1093494.

Conflict-of-interest statement: No conflicts of interest are reported by the authors or by any individuals in control of the content of this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Zhang H
L-Editor: Wang TQ
P-Editor: Zhang H

REFERENCES


Exome analysis for Cronkhite-Canada syndrome: A case report

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Abstract

BACKGROUND
Cronkhite-Canada syndrome (CCS) is a rare, non-genetic disorder characterized by multiple gastrointestinal polyps, and ectodermal lesions such as alopecia, fingernail atrophy, and skin mucosal pigmentation. Unfortunately, the pathogenesis of CCS is currently unknown.

CASE SUMMARY
Here, we describe the case of an elderly female with diarrhea, fatigue, and hair loss, who experienced abdominal pain for over half a year and was found to have multiple gastrointestinal polyps. She was diagnosed with CCS and was treated with albumin supplementation and prednisone, and her electrolyte imbalance was corrected. Following treatment, her symptoms significantly improved. To elucidate the role of potential genetic events in the pathogenesis of CCS, we performed exome sequencing using an extract of her colorectal adenoma.

CONCLUSION
Our data revealed multiple somatic mutations and copy number variations. Our findings provide a novel insight into the potential mechanisms of CCS etiology.
INTRODUCTION
Cronkite and Canada reported the first case of Cronkhite-Canada syndrome (CCS) in 1955, which was characterized by multiple gastrointestinal polyps, ectodermal lesions including alopecia, fingernail atrophy, and skin mucosal pigmentation[1]. Unfortunately, despite much research, the pathogenesis of CCS remains unknown. Some studies have reported an association between CCS and immune factors, especially infiltration of IgG4-positive plasma cells[2]. To date, there is no standard treatment for CCS; however, some studies have recommended glucocorticoid therapy for partial symptom relief[3]. Herein, we describe the case of an elderly female with the diagnosis of CCS. As part of her treatment regimen, she received albumin supplementation and prednisone, and her electrolyte disturbance was corrected. After 15 days, her symptoms, namely, hypokalemia and diarrhea, significantly improved. To elucidate the role of potential genetic events in the pathogenesis of CCS, we performed exome sequencing using DNA extracted from a colorectal adenoma. Our data revealed multiple somatic mutations and copy number variations. We are the first to identify 3 novel genetic mutations (USP24, KCNQ5, and FKBP10) in a CCS patient. Moreover, we demonstrated that the HPSE2, SPATA7, and ZC3H18 genes had markedly elevated copy numbers. Given this evidence, we hypothesized that these specific gene mutations and copy number variations are associated with the pathogenesis of CCS.

CASE PRESENTATION

Chief complaints
An elderly female patient sought treatment for diarrhea, fatigue, and hair loss, as well as abdominal pain for half a year at the Department of Gastroenterology on October 11, 2019.

History of present illness
She reported diarrhea 4-5 times daily, watery stools, no blood, and abdominal pain under the xiphoid process, not related to eating. Physical examination revealed obvious emaciation, alopecia, and nail atrophy.

History of past illness
Her past medical history is unremarkable.

Personal and family history
Her family history is unremarkable.

Physical examination
Physical examination revealed obvious emaciation, alopecia, and nail atrophy (Figure 1).

Laboratory examinations
Laboratory tests revealed the following: (routine blood examination) white blood cells: 10.03 × 10^9/L, hemoglobin: 95 g/L, and platelets: 151 × 10^9/L; (liver function) albumin 25 g/L; (electrolytes) Na+: 128 mmol/L, K+: 2.8 mmol/L.
Imaging examinations
She underwent gastroenteroscopy, which revealed multiple small polyps in the gastrointestinal tract (Figure 2).

Further diagnostic work-up
DNA samples: This study was performed in accordance with the guidelines of the Ethics Committee of the Mianyang Central Hospital. DNA was extracted from a sample of the patient's colonic adenomas and normal colon tissue. The samples were obtained via endoscopic mucosal resection and were preserved in liquid nitrogen.

Whole exome sequencing: Genomic DNA ≥ 1.5 μg from colonic adenomas and normal colon tissue was used for whole exome sequencing library construction. The Agilent liquid chip capture system was employed for the efficient enrichment of human DNA in all exon regions. Upon library construction, Qubit2.0 was used for preliminary quantification, and the library was diluted to 1 ng/μL. Subsequently, Agilent 2100 was utilized for detection of the library insert size to ensure library quality (the effective concentration of the library was > 2 nmol/L). Next, PE150 high-throughput sequencing was performed based on the Illumina Hiseq platform. Finally, the library and capture experiment were constructed using the Agilent SureSelect v5 kit, according to the manufacturer's instructions.

Quality control: Upon collection of the original sequenced reads (Sequenced Reads), Cutadapt software was used to remove the adapter and reads with N (N denotes that the base information cannot be determined) ratio ≥ 10%. In addition, the read pairs were discarded if the low-quality bases (quality score ≤ 5) accounted for 50% of the entire single read. Furthermore, quality controls (including, sequencing error rate distribution, base quality distribution, and GC content distribution) were performed, based on the selected filtered reads using the above methods.

Data analysis: The BWA (v0.7.15) software was used to map the sequenced reads to the human reference genome GRCh37 (hg19). Picard software was used to remove the sequence generated by PCR-duplication. The somatic single nucleotide variations (SNVs) and InDel detection were performed using the GATK (v4.1.0.0) and muTect2 software, respectively. The ANNOVAR software (Mon, 17 Jul 2017) was used to annotate gene mutations. Lastly, the control-free software (v11.4) was used for copy number variation analysis.

Exon sequencing results
Somatic mutation analysis, based on samples from the CCS patient, identified 47 SNVs. 75% of them were nonsynonymous SNVs. In addition, approximately 70% of them occurred in exonic regions (Figure 3). Mutations of the USP24, KCNQ5, and FKBP10 genes were identified as deleterious via SIFT, LRT, Polyphen2, and Mutation Taster software (Supplementary Table 1). Based on the COSMIC data, the three mutations in genes USP24, KCNQ5, and FKBP10 may be novel in CCS. The mutated genes are associated with the regulation of DNA-templated transcription (Figure 4). Our analysis showed that the HPSE2, SPATA7, and ZC3H18 genes had markedly elevated copy numbers, while other significant altered fragments were located in the intergenic regions (Table 1).
Table 1 The identified copy number alterations, as shown by exome sequencing

<table>
<thead>
<tr>
<th>Chr</th>
<th>Start</th>
<th>End</th>
<th>Gene</th>
<th>Copy number</th>
<th>Status</th>
<th>Wilcoxon rank sum test P value</th>
<th>Kolmogorov-Smirnov test P value</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>1.32E+08</td>
<td>1.32E+08</td>
<td>3</td>
<td>Gain</td>
<td>0.02315</td>
<td>0.14375</td>
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</tr>
<tr>
<td>3</td>
<td>37093599</td>
<td>37000000</td>
<td>3</td>
<td>Gain</td>
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<td>0.02719</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>29910395</td>
<td>30000000</td>
<td>3</td>
<td>Gain</td>
<td>0.01482</td>
<td>0.03778</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.37E+08</td>
<td>1.37E+08</td>
<td>3</td>
<td>Gain</td>
<td>0.03443</td>
<td>0.10684</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>98711799</td>
<td>99000000</td>
<td>HPSE2</td>
<td>3</td>
<td>Gain</td>
<td>0.0104</td>
<td>0.04592</td>
</tr>
<tr>
<td>11</td>
<td>73534113</td>
<td>74000000</td>
<td>1</td>
<td>Loss</td>
<td>0.00139</td>
<td>0.0043</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>8844244</td>
<td>88000000</td>
<td>SPATA7</td>
<td>3</td>
<td>Gain</td>
<td>0.02368</td>
<td>0.06465</td>
</tr>
<tr>
<td>16</td>
<td>3074297</td>
<td>3075822</td>
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<td>Gain</td>
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<tr>
<td>16</td>
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<td>89000000</td>
<td>ZC3H18</td>
<td>3</td>
<td>Gain</td>
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<td>0.00561</td>
</tr>
<tr>
<td>17</td>
<td>2274380</td>
<td>2276393</td>
<td>3</td>
<td>Gain</td>
<td>0.0146</td>
<td>0.03707</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>38702846</td>
<td>39000000</td>
<td>3</td>
<td>Gain</td>
<td>0.00017</td>
<td>0.00075</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>47287593</td>
<td>47000000</td>
<td>3</td>
<td>Gain</td>
<td>0.01445</td>
<td>0.03707</td>
<td></td>
</tr>
<tr>
<td>22</td>
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<td>28000000</td>
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<td>Gain</td>
<td>0.0032</td>
<td>0.00641</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>1456244</td>
<td>1486988</td>
<td>3</td>
<td>Gain</td>
<td>0.00126</td>
<td>0.0036</td>
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</tr>
<tr>
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<td>1</td>
<td>Loss</td>
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<td>0.00437</td>
<td></td>
</tr>
<tr>
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<td>59000000</td>
<td>3</td>
<td>Gain</td>
<td>0.01688</td>
<td>0.04401</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 Endoscopic characteristics of the patient with Cronkhite-Canada syndrome. A: The patient presented with multiple adenomas of the stomach greater curvature (blue arrow); B: The patient presented with multiple adenomas of the colon (blue arrow).

FINAL DIAGNOSIS

The patient was diagnosed with CCS.

TREATMENT

As part of her treatment regimen, she received albumin supplementation 10 g/d and prednisone 10 mg/d, and her electrolyte imbalance was corrected.
OUTCOME AND FOLLOW-UP

Treatment lasted for 15 d and her diarrhea, hypokalemia, and abdominal pain significantly improved.

DISCUSSION

Approximately 500 cases of CCS are currently described in the literature, with an estimated incidence of 1 in 1 million per year. The average age at CCS diagnosis is early 60s and it is predominantly diagnosed in males[4]. At present, there is no definite treatment plan for CCS. Previous literature reported that glucocorticoids and immunosuppression have certain benefits, and some studies reported that anti-tumor necrosis factor therapy is effective in CCS patients[5]. Our treatment plan and effect are consistent with these published works. However, there are limited studies on the pathogenesis of CCS. Therefore, based on the fact that CCS is an acquired non-genetic disease, we performed exon sequencing of excised diseased and non-diseased tissues from our CCS patient, in an attempt to elucidate CCS pathogenesis. Based on our exon sequencing results, three genes, namely, USP24, KCNQ5, and FKBP10 may be related to CCS pathogenesis.

We searched Human Gene Mutation Database (HGMD) and found that USP24 belongs to a large family of cysteine proteases that function as deubiquitinating enzymes. USP24 stabilizes the bromine domain protein and promotes malignant lung cancer[6]. In addition, Zhang L et al[7] found that USP24 deubiquitinase regulates DNA damage by directly targeting the tumor suppressor gene p53. Also, the USP24-Mcl-1 axis may represent a novel strategy in treating acute T cell lymphoma[8], whereas functional studies of the FKBP10 mutation reported an association with osteogenesis imperfecta[9]. The above two genes are both related to tumor formation and body development. Combined with the clinicopathological characteristics of CCS, we speculated that gene mutations are involved in the formation of multiple intestinal adenomas. The KCNQ family protein activates slowly during depolarization and forms heterogeneous channels with the protein encoded by KCNQ5 gene. KCN5 dependent potassium channels play an important role in airway smooth muscle relaxation[10]. Given the symptoms of diarrhea and difficult-to-correct hypokalemia of CCS, the KNQ3 mutation seems to suggest an association.

In terms of copy variation, ZC3H18 copy number losses are known to contribute to homologous recombination defects in high-grade serous ovarian cancers[11]. HPSE2 was reported to play an inhibitory role in bladder cancer[12]. Mutations in SPATA7 are associated with fundus macular degeneration[13]. CCS patients have multiple clinicopathological manifestations, such as, multiple gastrointestinal adenomas, nail atrophy, skin pigmentation, and alopecia, which may be related to the increased copy number of the three genes mentioned above.

However, due to the isolation of individual cases, the sample size of phenotypic alterations, caused by the above gene mutations, needs to be further expanded.

CCS is a rare disease and its etiology is unclear. The autoimmune etiology of CCS was previously proposed, and case reports described beneficial responses to immunosuppressive therapies such as azathioprine, anti-tumor necrosis factor antibodies, cyclosporine, and sirolimus[14,15]. Interestingly, Brigid S. Boland also conducted exome sequencing on tissue from a CCS patient who responded effectively to infliximab, and found that PRKDC mutations may be involved. However, this gene was not included in our analysis[14]. This suggests that the data on these mutations require further validation using tissues from a large CCS patient population.
CONCLUSION

In conclusion, we report a classic case of CCS, which was effectively treated with parenteral nutritional support and glucocorticoids, and we explored the pathogenesis of CCS from the perspective of gene mutation. Based on our analysis, we identified several gene mutations and alterations in gene copy numbers. However, we acknowledge that more genetic and epidemiological research is necessary to understand the complex pathogenesis of this rare but highly fatal disease.

FOOTNOTES

Author contributions: Li ZD and He YJ treated the patient and drafted the manuscript; Rong L and Ji YZ performed the exon sequencing work; Li X helped to search for references; Zhou SF and Li XA performed data retrieval and helped with drafting of the manuscript; all authors read and approved the final manuscript.

Informed consent statement: Informed consent was obtained from the patient’s family for publication of this case.

Figure 4 The functional attributes of mutated genes detected in an elderly female patient with Cronkhite-Canada syndrome.
report and any accompanying images.

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

**CARE Checklist (2016) statement:** This case report conforms to the CARE Checklist (2016) statement.

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**S-Editor:** Ma YJ
**L-Editor:** Webster JR
**P-Editor:** Ma YJ

**REFERENCES**


Discrepancy between non-invasive prenatal testing result and fetal karyotype caused by rare confined placental mosaicism: A case report

Zhen Li, Guang-Rui Lai

**Specialty type:** Medicine, research and experimental

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report’s scientific quality classification**
- Grade A (Excellent): 0
- Grade B (Very good): 0
- Grade C (Good): 0
- Grade D (Fair): 0
- Grade E (Poor): 0

**P-Reviewer:** Gislinge JIP, Denmark; Tolunay HE, Turkey

**Received:** December 14, 2021

**Peer-review started:** December 14, 2021

**First decision:** May 30, 2022

**Revised:** June 1, 2022

**Accepted:** July 18, 2022

**Article in press:** July 18, 2022

**Published online:** August 26, 2022

**Abstract**

**BACKGROUND**

Confined placental mosaicism (CPM) is one of the major reasons for discrepancies between the results of non-invasive prenatal testing (NIPT) and fetal karyotype analysis.

**CASE SUMMARY**

We encountered a primiparous singleton pregnant woman with a rare CPM consisting of 47,XY,+21; 47,XXY; and 46,XY, who obtained a false-positive result on NIPT with a high risk for trisomy 21. Copy-number variation sequencing on amniotic fluid cells, fetal tissue, and placental biopsies showed that the fetal karyotype was 47,XXY, while the placenta was a rare mosaic of 47,XY,+21; 47,XXY; and 46,XY.

**CONCLUSION**

The patient had a rare CPM consisting of 47,XY,+21; 47,XXY; and 46,XY, which caused a discrepancy between the result of NIPT and the actual fetal karyotype. It is important to remember that NIPT is a screening test, not a diagnostic test. Any positive result should be confirmed with invasive testing, and routine ultrasound examination is still necessary after a negative result.

**Key Words:** Non-invasive prenatal testing; Confined placental mosaicism; Copy-number variation sequencing; Karyotype analysis; Case report

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Core Tip: We identified that the patient had a rare confined placental mosaicism consisting of 47,XY,+21; 47,XXY; and 46,XY, which caused a discrepancy between non-invasive prenatal testing (NIPT) and fetal karyotype. Although NIPT has high sensitivity and specificity, false negatives and false positives are still possible. It is important to remember that NIPT is just a screening test, and any positive results need to be confirmed with invasive testing. Patients with negative NIPT results still require follow-up ultrasound examination.

INTRODUCTION

Currently, non-invasive prenatal testing (NIPT) using next-generation sequencing on a sample of cell-free fetal DNA (cffDNA) from maternal plasma is widely used as a screening test for common fetal aneuploidies (e.g., trisomy 21, 18, and 13; sex chromosome aneuploidies)[1]. This method of aneuploidy screening is not only non-invasive, but also highly accurate, with the sensitivity and specificity for pooled common aneuploidies as high as 99%[1,2]. NIPT offers higher accuracy when compared with serologic screening tests[3], thereby reducing the use of invasive diagnostic procedures that may result in miscarriage or intrauterine infection. However, NIPT is still a screening test and not a diagnostic test. As the cffDNA in maternal plasma originates from apoptotic placental trophoblast cells, it mainly consists of placental DNA[4,5], and the results may not represent the actual fetal karyotype. One of the most common reasons for false results on NIPT is a confined placental mosaicism (CPM)[6]. We report our experience with a patient whose NIPT result indicated a high risk for trisomy 21, but in whom the actual fetal karyotype was 47,XXY. The reason for this discrepancy was the presence of a CPM; the placenta was a rare mosaic of 47,XY,+21; 47,XXY; and 46,XY.

CASE PRESENTATION

Chief complaints
The patient was a 26-year-old primiparous woman with a singleton pregnancy. At 15 + 1 wk, the second-trimester serologic screening showed an elevated risk for Down’s syndrome, at 1 in 146 [alpha-fetoprotein: 0.67 multiples of the median (MoM); free β human chorionic gonadotropin: 3.18 MoM; unconjugated estradiol: 0.76 MoM]. The patient requested further testing.

History of present illness
The patient has no present illness.

History of past illness
The patient has no past illness.

Personal and family history
The patient denied any personal or family history.

Physical examination
The patient’s basic vital signs were within normal limits. She requested NIPT before amniocentesis.

Laboratory examinations
Maternal plasma was collected for NIPT at 15 + 3 wk. We followed the standard method for performing NIPT, which has been described previously[7]. The NIPT results showed a high risk for trisomy 21, with a Z-score of 16.21 for chromosome 21; however, there was a low risk for sex chromosome aneuploidy (the Z-score of chromosome X and Y was -12.88 and 79.64, respectively).

To confirm the positive NIPT results, amniocentesis was performed at 19 + 2 wk. Copy-number variation sequencing (CNV-seq) and karyotype analysis performed on amniotic fluid cells suggested that the fetal karyotype was XXY, as shown in Figures 1 and 2 and Table 1. The patient underwent genetic counseling and decided to terminate her pregnancy. After written informed consent for the procedure and further testing was obtained, she underwent an induced abortion at 22 + 5 wk. Samples
### Table 1: Results of copy-number variation sequencing

<table>
<thead>
<tr>
<th>Sample type</th>
<th>Sample</th>
<th>Result of CNV-seq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amniotic fluid</td>
<td>Amniotic fluid cells</td>
<td>47,XXY</td>
</tr>
<tr>
<td>Fetal tissue</td>
<td>Fetal muscle tissue</td>
<td>47,XXY</td>
</tr>
<tr>
<td>Umbilical cord</td>
<td>Middle segment of umbilical cord</td>
<td>47,XXY</td>
</tr>
<tr>
<td>Placenta</td>
<td>Center of fetal face</td>
<td>47,XY,+21[65%]/46,XY[35%]</td>
</tr>
<tr>
<td></td>
<td>Margin of fetal face</td>
<td>47,XY,+21[65%]/46,XY[35%]</td>
</tr>
<tr>
<td></td>
<td>Margin of maternal face</td>
<td>47,XY,+21[65%]/46,XY[35%]</td>
</tr>
<tr>
<td></td>
<td>Center of maternal face</td>
<td>47,XY,+21[60%]/47,XXY[20%]/46,XY[20%]</td>
</tr>
<tr>
<td></td>
<td>Placental center</td>
<td>47,XY,+21[65%]/47,XXY[10%]/46,XY[25%]</td>
</tr>
</tbody>
</table>

CNV-seq: Copy-number variation sequencing.

---

**Figure 1** The fetal karyotype performed on cultured amniotic fluid cells.

---

from the fetus were collected after delivery - including fetal muscle tissue, the middle segment of the umbilical cord, and placental tissue - and sent for CNV-seq. The placental samples included a mid-thickness section from the center of the placenta and samples from the center and margin of the maternal face, and the center and margin of the fetal face. As shown in Table 1 and Figure 2, the fetal muscle tissue and umbilical cord tissue had a karyotype of 47,XXY - matching that of the amniotic fluid cells. However, the center and margin samples from the fetal face and the margin of the maternal face of the placenta had a mosaic karyotype of 47,XY,+21 (65%) and 46,XY (35%), respectively. The mid-thickness sample from the placental center and the sample from the center of the maternal face of the placenta demonstrated a mosaic of 47,XY,+21; 47,XXY; and 46,XY with different proportions in each sample. In brief, the placenta was a mosaic of 47, XY,+21; 47,XXY; and 46,XY.

**Imaging examinations**

No obvious abnormality was detected upon fetal ultrasonography.

---

**FINAL DIAGNOSIS**

The fetal karyotype was 47,XXY; whereas the placenta was a mosaic of 47,XY,+21; 47,XXY; and 46,XY.

---

**TREATMENT**

Amniocentesis was used to determine the karyotype of the fetus. A placental sample was collected
Figure 2 The copy-number variation sequencing results in different samples. A: Amniotic fluid cells, fetal muscle and umbilical cord suggested the fetal karyotype was 47,XXY; B: The placenta of fetal face (both center and margin) and margin of maternal face showed a 47,XY,+21/46,XY mosaic; C and D: The
following induced abortion and was tested to determine the cause of the discrepancy between the NIPT results and the fetal karyotype.

OUTCOME AND FOLLOW-UP

The patient underwent an induced abortion after genetic counseling. The timeline is shown in Table 2.

DISCUSSION

The patient had a rare CPM consisting of 47,XY,+21; 47,XXY; and 46,XY, which caused a discrepancy between the results of NIPT and the actual fetal karyotype. The cfDNA in maternal blood has a dominant peak size of 143 base pairs, which is shorter than the free DNA fragments typically found in maternal plasma (around 166 base pairs)[8]. cfDNA can be detected as early as 4.5 wk of pregnancy[9], is present throughout pregnancy, and disappears from the maternal circulation within hours after delivery[10]. The proportion of cfDNA to total free DNA (fetal and maternal) is referred to as the fetal fraction, and it increases throughout pregnancy. At 10-20 wk of gestation, the average fetal fraction in maternal plasma is 10%-15%; however, it may range from less than 3% to over 30%[11].

The introduction of NIPT in the late 2000s was revolutionary for aneuploidy screening, and it is now a commonly used screening method. The sensitivity and positive predictive value of serologic screening for trisomy 21 is only about 80% and 5%, respectively[3]; while the sensitivity of NIPT can reach up to 99%, with a positive predictive value of 94.5%[1]. Thus, the expanded use of NIPT can greatly reduce the use of invasive diagnostic procedures, thereby avoiding the resulting complications of miscarriage or intrauterine infection. The sensitivity and specificity of NIPT for other common aneuploidies, including trisomy 18, trisomy 13, and sex chromosome aneuploidy, are as high as 99%[1]. However, false positive and false negative results for NIPT occur at a rate of 0.3% and 1.1%, respectively[1]. There are four factors that affect the results of NIPT: (1) A low fetal fraction, which can be present in overweight mothers, usually leading to a false negative result[12]; (2) Maternal conditions, such as the presence of a tumor, mosaicism, or chromosomal abnormalities, are often associated with false-positive results[13]; (3) Fetal chimerism and vanishing twin syndrome can affect the results[14]; and (4) CPM, which is also a very common cause of incorrect results[6,15]. In our patient with CPM, the results of NIPT were falsely positive for trisomy 21 and falsely negative for 47,XXY.

The mosaicism involved in CPM occurs only in the placenta, not in the fetus. In most situations, the fetal outcome is normal if the fetal chromosomes are normal[16]. However, 10% of pregnancies that involve a placenta with CPM are affected by fetal growth restriction, even after constitutional fetal chromosomal abnormalities are excluded[17,18]. According to a large-scale evaluation of chorionic villus sampling, the prevalence of CPM is about 0.6% to 1.0%[18,19]. Although the genetic makeup of placental and fetal tissue is usually identical, clinicians should be mindful of the possibility of CPM, especially as it accounts for a high proportion of incorrect results on NIPT[6]. Wu et al[20] found that CPM was present in 6 of 10 placentas from pregnancies in which there was a false-positive result on NIPT[20]. Our group identified three false negative NIPT results in a total of 34311 pregnancies, and all fetuses had structural abnormalities detected on follow-up ultrasound screening. Placental biopsies were collected from 2 of the 3 patients with false-negative NIPT results; both were confirmed to have CPM. One was the patient described in this report, and the other patient had a fetus with trisomy 21 and a placental mosaic of 47,XY,+21 and 46,XY.

There are two key elements that should be noted for NIPT. While its sensitivity and specificity are high, the positive predictive value varies from 94.5% for trisomy 21[21], to 82.1% for trisomy 18, 46.2% for trisomy 13, and 46.7% for sex chromosome aneuploidies[1]. A positive result on NIPT should always be confirmed with invasive testing (e.g., amniocentesis, umbilical cord blood sampling, chorionic villus sampling) before any irreversible procedure is performed, as the results on NIPT may not correlate with the true fetal genotype[16]. The other key element is that false-negative results on NIPT are associated with more serious consequences than false-positive results and cause more stress to pregnant women and their families. Majorly, the false-negative result can be proven when abnormalities are detected on routine follow-up ultrasound screening which is still necessary, even when the results of NIPT are normal. Attention should also be paid to low fetal fractions. The quality threshold for the fetal fraction is commonly accepted as 4%, and samples with values below this are often reported as having inconclusive results[11].

Table 2

<table>
<thead>
<tr>
<th>Gender</th>
<th>Chromosome</th>
<th>Maternal Age</th>
<th>CPM Type</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>47,XY,+21</td>
<td>33</td>
<td>Yes</td>
<td>Yes</td>
<td>Normal</td>
</tr>
<tr>
<td>Female</td>
<td>47,XXY</td>
<td>34</td>
<td>No</td>
<td>No</td>
<td>False</td>
</tr>
<tr>
<td>Male</td>
<td>46,XY</td>
<td>32</td>
<td>Yes</td>
<td>Yes</td>
<td>Normal</td>
</tr>
</tbody>
</table>

The patient underwent an induced abortion after genetic counseling. The timeline is shown in Table 2.
Table 2 Timeline for the care

<table>
<thead>
<tr>
<th>Gestational age (wk)</th>
<th>Examination items</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 + 1</td>
<td>Serum Down’s screening</td>
<td>High risk for trisomy 21</td>
</tr>
<tr>
<td>15 + 3</td>
<td>NIPT</td>
<td>High risk for trisomy 21, low risk for sex chromosome aneuploidy</td>
</tr>
<tr>
<td>19 + 2</td>
<td>Amniocentesis (CNV-seq and karyotype analysis)</td>
<td>47,XXY</td>
</tr>
<tr>
<td>22 + 5</td>
<td>Abortion, collected fetal muscle tissue, umbilical cord and placental samples</td>
<td>Fetal muscle tissue and umbilical cord: 47,XXY; placenta: A mosaic of 47,XY,+21; 47,XXY; and 46,XY</td>
</tr>
</tbody>
</table>

NIPT: Noninvasive prenatal testing; CNV-seq: Copy-number variation sequencing.

CONCLUSION

We describe our experience with a rare discrepancy between NIPT and karyotype testing. It is important to remember that NIPT is just a screening test, and any positive result should be confirmed with invasive testing. Patients with negative results on NIPT still require follow-up ultrasound examination.

ACKNOWLEDGEMENTS

Thanks for the patients’ family participation.

FOOTNOTES

Author contributions: Li Z provided obstetrical service, collected samples and wrote the paper; Lai GR did the examinations, genetic consult and revised the paper.

Supported by the 345 Talent Project of Shengjing Hospital, No. M0298.

Informed consent statement: All participants were fully informed of the study with written consent obtained from each participant. They gave consent for their de-identified personal or clinical details to be published in this study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

REFERENCES

61ra91 [PMID: 22509971 DOI: 10.1517/14712598.2012.670632]
Paroxysmal speech disorder as the initial symptom in a young adult with anti-N-methyl-D-aspartate receptor encephalitis: A case report

Chuan-Chen Hu, Xiao-Ling Pan, Mei-Xia Zhang, Hong-Fang Chen

Specialty type: Neurosciences

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Huan C, United States; Kreisel W, Germany; Pitton Rissardo J, Brazil; Ullah K, Pakistan

Received: January 19, 2022
Peers-review started: January 19, 2022
First decision: April 8, 2022
Revised: April 22, 2022
Accepted: July 22, 2022
Article in press: July 22, 2022
Published online: August 26, 2022

Abstract

BACKGROUND
Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a treatable but frequently misdiagnosed autoimmune disease. Speech dysfunction, as one of the common manifestations of anti-NMDAR encephalitis, is usually reported as a symptom secondary to psychiatric symptoms or seizures rather than the initial symptom in a paroxysmal form. We report a case of anti-NMDAR encephalitis with paroxysmal speech disorder as a rare initial manifestation, and hope that it will contribute to the literature.

CASE SUMMARY
A 39-year-old man with anti-NMDAR encephalitis initially presented with paroxysmal nonfluent aphasia and was misdiagnosed with a transient ischemic attack and cerebral infarction successively. The patient subsequently presented with seizures, but no abnormalities were found on brain magnetic resonance imaging or electroencephalogram. Cerebrospinal fluid (CSF) analysis revealed mild pleocytosis and increased protein levels. Anti-NMDAR antibodies in serum and CSF were detected for a conclusive diagnosis. After immunotherapy, the patient made a full recovery.

CONCLUSION
This case suggests that paroxysmal speech disorder may be the presenting symptom of anti-NMDAR encephalitis in a young patient.

Key Words: Anti-N-methyl-D-aspartate receptor encephalitis; Autoimmune disease; Paroxysmal speech disorder; Seizure; Immunotherapy; Case report

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Core Tip: Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a treatable but often misdiagnosed autoimmune disease. In this paper, we describe a 39-year-old man with anti-NMDAR encephalitis who initially presented with paroxysmal speech disorder and was subsequently misdiagnosed with a transient ischemic attack and cerebral infarction. The definitive diagnosis was made based on the detection of anti-NMDAR antibodies in serum and cerebrospinal fluid. The patient recovered completely after immunotherapy. This case suggests that paroxysmal speech disorder may be the first symptom of anti-NMDAR encephalitis in a young patient without risk factors for cerebrovascular disease.

Citation: Hu CC, Pan XL, Zhang MX, Chen HF. Paroxysmal speech disorder as the initial symptom in a young adult with anti-N-methyl-D-aspartate receptor encephalitis: A case report. World J Clin Cases 2022; 10(24): 8648-8655
URL: https://www.wjgnet.com/2307-8960/full/v10/i24/8648.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i24.8648

INTRODUCTION
Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was initially reported as a paraneoplastic immune-mediated syndrome associated with ovarian teratoma[1]. Since Dalmau et al.[2] discovered antibodies against N-methyl-D-aspartate receptor (NMDAR) in 2007, anti-NMDAR encephalitis has been gradually recognized worldwide. The exact incidence of the disease was unknown. A multicenter, population-based prospective study suggested that anti-NMDAR encephalitis accounts for 4% of all causes of encephalitis[3]. Data from the California Encephalitis Project regarding the cause of encephalitis revealed that the frequency of anti-NMDAR encephalitis surpassed that of individual viral etiologies in young individuals[4]. Anti-NMDAR encephalitis is a treatable but often misdiagnosed autoimmune disease[5]. It primarily affects children and young adults (a median age of 21 years), with a higher incidence among females (4:1) but a similar incidence between women and men after the age of 45 years[6]. We present a case of anti-NMDAR encephalitis with paroxysmal speech disorder as the presenting symptom. The patient was initially misdiagnosed with cerebrovascular disease due to a transient ischemic attack (TIA)-like onset, but anti-NMDAR antibodies in serum and cerebrospinal fluid (CSF) eventually validated the diagnosis.

CASE PRESENTATION

Chief complaints
A 39-year-old man presented to the emergency department of our hospital complaining of repeated episodes of speech impediment for one day. In addition, he experienced a generalized tonic-clonic seizure an hour before the visit.

History of present illness
The patient's symptoms began with paroxysmal speech disorder one day prior. Each attack lasted for dozens of seconds to several minutes and was not accompanied by other neurological deficits. The patient experienced convulsion with loss of consciousness during his first visit to another hospital. The epileptic attack lasted for two minutes and the patient regained consciousness after ten minutes. He was diagnosed with TIA and treated with 200 mg aspirin and 20 mg atorvastatin. Then, he presented to our hospital with persistent slurred speech lasted for more than one hour.

History of past illness
Except for a headache one month prior, the patient had no significant medical history and no drug in use.

Personal and family history
The patient's personal and family history was unremarkable.

Physical examination
The patient's temperature was 36.5 °C, heart rate was 89 beats per minute, respiratory rate was 18 breaths per minute, blood pressure was 18.1/9.8 KPa and oxygen saturation in room air was 98%. No obvious abnormality was found on neurological examination when he was admitted to another hospital. However, we found nonfluent aphasia and deviation of the tongue to the right on neurological
examination.

**Laboratory examinations**
Routine laboratory studies, including a complete blood count, hepatic and renal function, blood glucose, glycosylated hemoglobin, coagulation testing, autoantibodies, autoantibody spectrum associated with anti-cardiolipin antibodies, thyroid function, homocysteine, serum tumor markers, human immunodeficiency virus antibody test and treponema pallidum hemagglutination assay, were all unremarkable.

**Imaging examinations**
An initial brain computed tomography (CT) scan showed no significant abnormalities. Brain computed tomography angiography (CTA) showed no intracranial hemorrhage, aneurysm, vascular malformation, or intracranial arterial stenosis. Brain magnetic resonance imaging (MRI) further excluded lesions that were easily overlooked on CT. Based on the above imaging findings, ischemic stroke was ruled out.

**Electrophysiological detection**
Routine and ambulatory electroencephalogram (EEG) showed no epileptic discharges, and the diagnosis of epilepsy was untenable.

**Further diagnostic work-up**
Lumbar puncture revealed a CSF pressure of 2.21 kPa. CSF analysis revealed a nucleated cell count of 28/μL (normal < 5/μL), which was dominated by lymphocytes (85% lymphocytes, 10% monocytes, 4% neutrophils, 1% eosinophils), lactate dehydrogenase of 56 U/L (normal < 40 U/L), and protein levels of 662 mg/L (normal 120-600 mg/L). The concentrations of glucose, chloride and adenosine deaminase in the CSF were normal. Anti-NMDAR antibodies were detected in the CSF and serum by indirect immunofluorescence testing using a commercial kit (Euroimmune, Germany). The titer of anti-NMDAR antibody IgG was 1:10 (++) in CSF and 1:32 (++) in serum. Anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 1, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 2, gamma-aminobutyric acid-B, leucine-rich glioma-inactivated protein 1, contactin-associated protein-like 2 and glutamic acid decarboxylase-65 antibodies IgG in CSF and serum were negative. No tumor was found on chest CT or abdominal ultrasound.

**FINAL DIAGNOSIS**
The presence of anti-NMDAR antibodies in serum and CSF led to a final diagnosis of anti-NMDAR encephalitis in the presented case.

**TREATMENT**
The patient was initially misdiagnosed with TIA and treated with 200 mg aspirin and 20 mg atorvastatin at another hospital. The patient was subsequently misdiagnosed with cerebral infarction and received intravenous thrombolytic therapy with 50 mg of recombinant tissue plasminogen activator at the emergency department of our hospital. Twenty-four hours after thrombolytic therapy, aspirin (200 mg/d) and atorvastatin (20 mg/d) were administered orally in the ward until the final diagnosis was reached.

Ultimately, the patient was diagnosed with anti-NMDAR encephalitis and treated with intravenous immunoglobulin (25 g/d × 5 d) and intravenous methylprednisolone (1000 mg/d × 3 d to 500 mg/d × 3 d to 240 mg/d × 3 d to 120 mg/d × 3 d). Then the patient was discharged with slowly tapered oral methylprednisolone (48 mg qd × 2 wk to reduction of the dosage by 4 mg every 2 wk) (Figure 1).

**OUTCOME AND FOLLOW-UP**
The patient’s speech disorder recovered after immunotherapy, and he no longer had seizures. No adverse effect was observed during the treatment. At the follow-up six months after discharge, he was asymptomatic.
The NMDAR is a member of the ionotropic glutamate receptor family, which plays a crucial role in neuronal communication\[7\]. NMDAR-mediated signals control diverse processes across the life course, including synaptogenesis and synaptic plasticity, and contribute to excitotoxic processes in neurological disorders\[8\]. NMDAR overactivity is the proposed underlying mechanism in epilepsy, dementia, and stroke, whereas decreased NMDAR activity results in symptoms of schizophrenia\[9\]. The antibodies in patients with anti-NMDAR encephalitis lead to selective and reversible loss of cell-surface NMDARs by capping and internalization, resulting in abrogation of NMDAR-mediated synaptic function, which can cause patients’ symptoms, such as psychotic behavior, signs of involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements, tremor) and autonomic dysfunction (cardiac dysrhythmia, hypertension, hypersalivation)\[10,11\].

Anti-NMDAR encephalitis is the most common cause of treatable autoimmune diseases and is characterized by prominent neuropsychiatric symptoms\[12\]. The clinical symptoms of the disease are mainly classified into eight groups: Psychiatric and behavioral symptoms, seizures, motor dysfunctions/involuntary movements, memory deficits, speech disorders, decreased levels of consciousness, autonomic dysfunctions and central hypoventilation\[13\]. Symptom presentations vary between children and adults; neurologic symptoms occur more often in children, while psychiatric symptoms are prevalent in adults\[14\], but in most cases, the progression of symptoms evolves toward a similar syndrome in days or weeks\[6\].

According to literature evaluations, over half of the patients with anti-NMDAR encephalitis had abnormal speech, including reduced verbal output or mutism, abnormal content, mumbling, echolalia, increased output or perseveration\[15,16\]. Speech dysfunction is one of the common symptoms of anti-NMDAR encephalitis but is frequently described as a symptom secondary to psychiatric symptoms or seizures rather than the main or initial symptom\[17\]. To our knowledge, paroxysmal speech disturbance as the first presentation has rarely been reported in anti-NMDAR encephalitis. Finke et al\[18\] described a patient with anti-NMDAR encephalitis who presented with recurrent aphasia. Episodes were accompanied by headache, hemianopia, and hemiparesis with pleocytosis, mimicking the syndrome of headache with neurological deficits and CSF lymphocytosis (Table 1). The patient in our report had recurrent speech dysfunction at onset but without typical psychiatric symptoms or movement disorders. Therefore, he was originally misdiagnosed with TIA and then with cerebral infarction due to his symptom lasting for more than one hour. Since brain MRI showed no structural abnormalities, we
Hu CC et al. Paroxysmal speech disorder of anti-NMDAR encephalitis

| Table 1 Comparing the present case with that from Finke et al[18] |
|----------------|-----------------|----------------|
| Item           | The present case | Finke et al[18] |
| Age (yr)       | 39              | 67             |
| Gender         | Male            | Male           |
| History of past illness | No              | Migraine with aura |
| Vascular risk factors | No              | No             |
| Initial paroxysmal symptoms | Nonfluent aphasia | Right homonymous hemianopia, global aphasia and right hemiparesis |
| Accompanying symptoms | Generalized tonic-clonic seizures | Throbbing bilateral headaches, confusion and agitation |
| CSF analysis   | Mild pleocytosis (28 cells/μL) dominated by lymphocytes (85%) and elevated protein (662 mg/L) | Lymphocytic pleocytosis (95 cells/mL) with few activated lymphocytes and plasma cells and elevated protein (96 mg/dL) |
| Brain MRI      | No lesions      | Mild frontoparietal microangiopathic leukoencephalopathy |
| EEG            | No epileptic discharges | First: Moderate generalized slowing; r: Normal |
| Tumor screening| Negative        | Negative       |
| Testing for anti-NMDAR antibodies | IgG NMDAR antibodies in both CSF (titer, 1:10) and serum (titer, 1:32) | IgG NMDAR antibodies in CSF (titer, 1:32), but not serum |
| Treatment      | Intravenous immunoglobulin and methylprednisolone, followed by oral methylprednisolone | Oral corticosteroids and plasma exchange, followed by azathioprine |
| Outcome        | Asymptomatic    | No further episodes occurred, but verbal long-term memory deficit persisted |

| MRI: Magnetic resonance imaging; CSF: Cerebrospinal fluid; EEG: Electroencephalogram; NMDAR: N-methyl-D-aspartate receptor. |

considered that paroxysmal speech disorder might be a form of seizure. However, subsequent EEG recorded no epileptic discharges. The hypothesis was disproved.

This case deserves our attention as we consider the diagnostic and treatment options. First, this patient was a young adult with no risk factors for cerebrovascular disease (e.g., hypertension, diabetes, cardiopathy, etc.) and no abnormalities on brain CTA. Furthermore, this patient had a headache a month before onset, which is exactly one of the common prodromal symptoms of anti-NMDAR encephalitis. Finally, the patient had a seizure during the visit, which is seldom observed in ischemic stroke but is a common symptom of anti-NMDAR encephalitis.

To date, the pathophysiological mechanism of speech impairments caused by anti-NMDAR encephalitis remains unclear. Hébert et al[17] reported a case of adult-onset anti-NMDAR encephalitis presenting primarily as progressive nonfluent aphasia. The patient's EEG showed the left fronto-temporal slow wave activity, suggesting that the function of left frontal and opercular structures might be affected. Constantinides et al[19] described a case of an adult patient with anti-NMDAR encephalitis presenting with isolated, abrupt-onset aphasia. The patient's EEG revealed paroxysmal left temporal theta and delta waves. Deiva et al[20] reported a child with anti-NMDAR encephalitis who presented sudden and isolated Broca's aphasia following partial seizures and whose sleep EEG showed a repetitive pattern of focal theta rhythms spreading through the left hemisphere (Table 2). Similar electrical patterns were also described in previous anti-NMDAR encephalitis studies[21,22]. These studies suggested that these patterns did not necessarily correlate with seizures[17,21] but were probably the result of an increased fronto-temporal-to-occipital gradient in cerebral glucose metabolism due to impaired NMDAR function[22]. Unfortunately, similar EEG abnormalities were not found in our case. However, the EEGs of the reported cases of anti-NMDAR encephalitis with aphasia provided neurophysiological evidence of left focal cortical dysfunction. Finke et al[18] speculated that cortical spreading depression (CSD) might be related to the patient's transient neurological symptoms. According to their hypothesis, CSD can be experimentally induced by glutamate, and it is assumed that an antibody-mediated decrease in NMDAR leads to increased glutamatergic activity by inactivating GABAergic neurons[10,18].

From previous observations, approximately 90% of anti-NMDAR encephalitis patients had at least four symptoms by the fourth week of disease onset[6], and mono- or oligosymptomatic presentations of anti-NMDAR encephalitis were rare[6,10]. The atypical manifestations of our case might be due to early initiation of immunotherapy, which prevented the development of the complete clinical phenotype of anti-NMDAR encephalitis[18].
Hu CC et al. Paroxysmal speech disorder of anti-NMDAR encephalitis

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>29</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Isolated, abrupt-onset aphasia</td>
<td>A progressive nonfluent aphasia; simple partial seizures; confusable and emotional lability</td>
<td>Fever; repeated right partial motor seizures; sudden and isolated Broca’s aphasia</td>
</tr>
<tr>
<td>Description of language difficulties</td>
<td>With a 6-mo history of aphasia; her prominent impairment, namely, non-fluent aphasic disturbances (effortful, halting speech with sound errors), had progressed rapidly and reached a peak in 72 h, at which point she was unable to speak and had difficulties in writing, but her ability to perceive verbal stimuli was relatively preserved</td>
<td>6-d history of progressive word-finding difficulties</td>
<td>The patient suddenly presented isolated speech difficulties; speech evaluation showed that her receptive language was preserved but that expressive language was affected associated with anoma, and anarthria suggestive of Broca’s aphasia</td>
</tr>
<tr>
<td>EEG</td>
<td>Paroxysmal left temporal theta and delta waves</td>
<td>Abundant intermittent polymorphic slow wave activity over the left lateral fronto-temporal area</td>
<td>Waking EEG was characterized by unilateral left hemispheric slowing, and sleep EEG showed a repetitive pattern of focal theta rhythms over 10-15 s in the postero-temporal region which then spread to the whole left hemisphere for 45-60 s</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>CSF analysis</td>
<td>Within normal limits (1 white blood cells $\times 10^4$/L, protein 420 g/L), with negative cytology</td>
<td>Within normal limits (2 white blood cells $\times 10^4$/L, 95% lymphocytes, protein 0.20 g/L, glucose 3.7 mmol/L) with normal cytology</td>
<td>19 leukocytes, with 0.22 g/L of protein and no oligoclonal bands</td>
</tr>
<tr>
<td>Testing for anti-NMDAR antibodies</td>
<td>Positive in both serum and CSF</td>
<td>Positive in CSF</td>
<td>Positive (1:100) in both serum and CSF</td>
</tr>
<tr>
<td>Screening for ovarian teratoma</td>
<td>Negative</td>
<td>A 5.3 cm right adnexal cystic teratoma (confirmed by pathology)</td>
<td>Negative</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>A 5-d course of intravenous methylprednisolone 1 g/d, followed by slowly tapered oral methylprednisolone 1 mg/kg per day; six courses of plasmapheresis; azathioprine 50 mg bid</td>
<td>A 2d course of 2 mg/kg intravenous immunoglobulin</td>
<td>Intravenous rituximab (375 mg/m²)</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Aphasia eventually resolved at the 1 yr follow-up</td>
<td>10 mo after symptom onset, her language impairments completely resolved, but she had impaired recollection of the events surrounding her hospitalization</td>
<td>After 20 mo of follow-up, the child had completely recovered and was free of seizures</td>
</tr>
</tbody>
</table>

EEG: Electroencephalogram; MRI: Magnetic resonance imaging; CSF: Cerebrospinal fluid; NMDAR: N-methyl-D-aspartate receptor.

On physical examination, the patient's tongue deviated to the right when he was asked to extend it. As no involuntary movements of the patient's jaw, mouth, tongue, or lower face were observed, the phenomenon was thought to be functional or central hypoglossal palsy rather than oromandibular dystonia or orofacial dyskinesia.

No lesion was found on our patient's brain MRI scan. A systematic review indicated that MRI scans showed abnormal findings in less than 50% of patients with anti-NMDAR encephalitis[23]. The CSF test revealed a slight increase in cell count and protein. Dalmau et al[11] reported that 95% of patients had CSF abnormalities, 91% had a mild-to-moderate lymphocytic increase, and 32% had a mildly elevated level of protein. Anti-NMDAR encephalitis was diagnosed based on the clinical manifestations, evidence of CSF, brain MRI, EEG and the antibodies against the NRI subunit of the NMDAR in CSF and/or serum[13]. Speech impairment and seizures, as well as positive anti-NMDAR IgG antibodies in CSF and serum, led to the patient's ultimate diagnosis. Despite the severity of anti-NMDAR encephalitis, patients tend to have a good prognosis after immunotherapy[8]. Our patient made a full recovery after intravenous immunoglobulin and steroid administration. Therefore, early diagnosis and immunotherapy are important to patients with anti-NMDAR encephalitis.

The present report describes a young patient with a peculiar initial manifestation, and it demonstrates that a patient with anti-NMDAR encephalitis can present solely paroxysmal speech dysfunction with no additional symptoms of limbic encephalitis at onset. This case may also help us to further understand...
the manifestation of speech dysfunction in patients with anti-NMDAR encephalitis. The likelihood of anti-NMDAR encephalitis should be considered in a young adult with paroxysmal speech disorder and clinical features of limbic encephalitis, such as psychiatric disorders, seizures, and cognitive impairment.

CONCLUSION

This case suggests that paroxysmal speech disorder may be the first symptom of anti-NMDAR encephalitis in a young patient without risk factors for cerebrovascular disease. Recognizing that is vital to early diagnosis and more timely treatment for future cases.

ACKNOWLEDGEMENTS

We sincerely thank the patient involved in this paper.

FOOTNOTES

Author contributions: Hu CC wrote the manuscript; Zhang MX was responsible for data acquisition; Pan XL revised the manuscript; Chen HF followed the patient during treatment and contributed to the conception of the paper; and all authors granted final approval for the version to be submitted.

Informed consent statement: Informed consent was obtained verbally from the patient for publication of this report.

Conflict-of-interest statement: The authors have no conflict of interest to declare.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

REFERENCES


6 Titulaer MJ, McCracken L, Gabilondo I, Armandegi T, Glaser C, Izuuka T, Honig LS, Benseler SM, Kawachi I, Martinez-
Hu CC et al. Paroxysmal speech disorder of anti-NMDAR encephalitis


CASE REPORT

Anesthetics management of a renal angiomyolipoma using pulse pressure variation and non-invasive cardiac output monitoring: A case report

Woo Jae Jeon, Woo Jong Shin, Young Joon Yoon, Chan Woo Park, Jae Hang Shim, Sang Yun Cho

BACKGROUND
Hypovolemic shock can lead to life-threatening organ dysfunction, and adequate fluid administration is a fundamental therapy. Traditionally, parameters such as vital signs, central venous pressure, and urine output have been used to estimate intravascular volume. Recently, pulse pressure variation (PPV) and non-invasive cardiac monitoring devices have been introduced. In this case report, we introduce a patient with massive active bleeding from giant renal angiomyolipoma (AML). During emergent nephrectomy, we used non-invasive cardiac monitoring with CSN-1901 (Nihon Kohden, Tokyo, Japan) and PPV to evaluate the patient's intravascular volume status to achieve optimal fluid management.

CASE SUMMARY
A 30-year-old male patient with giant AML with active bleeding was referred to the emergency room complaining of severe abdominal pain and spontaneous abdominal distension. AML was diagnosed by computed tomography, and emergent nephrectomy was scheduled. Massive bleeding was expected so we decided to use non-invasive cardiac monitoring and PPV to assist fluid therapy because they are relatively easy and fast compared to invasive cardiac monitoring. During the surgery, 6000 mL of estimated blood loss occurred. Along with the patient's vital signs and laboratory results, we monitored cardiac output, stroke volume, stroke volume index with a non-invasive cardiac monitoring device, and PPV using an intra-arterial catheter to evaluate intravascular volume status of the patient to compensate for massive bleeding.

CONCLUSION
In addition to traditional parameters, non-invasive cardiac monitoring and PPV are useful methods to evaluate patient's intravascular volume status and provide...
guidance for intraoperative management of hypovolemic shock patients.

**Key Words:** Renal angiomyolipoma; Pulse pressure variation; Cardiac output; Case report

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**Core Tip:** We present a giant ruptured renal angiomyolipoma (> 20 cm) with active bleeding. Emergent operation was performed. The successful fluid management was carried with pulse pressure variation and noninvasive cardiac output monitoring.

**INTRODUCTION**

Angiomyolipoma (AML) is a benign tumor of the kidney that accounts for up to 3% of all renal masses [1]. Most of these masses are sporadic and incidentally diagnosed. However, large AMLs (> 4 cm) can present with symptoms such as hemorrhage, pain, a palpable mass and mass-associated symptoms. Giant AMLs > 20 cm in size are rare, and few cases have been reported. Enlarging giant AMLs can produce an aneurysm that can rupture and lead to massive peri-renal bleeding and hypovolemic shock, a condition known as Wunderlich syndrome [2]. The dynamic parameters of fluid responsiveness are related to cardiopulmonary interactions under general anesthesia with mechanical ventilation. Pulse pressure variation (PPV) has shown great advantage to optimize hemodynamic parameters using physiological data from non-invasive means. PPV can assist with fluid administration and hemodynamic stability in patients under general anesthesia receiving mechanical ventilation [3]. We used a CSM-1901 (Nihon Kohden, 15-Tokyo, Japan) to non-invasively monitor the patient’s cardiac output (CO), stroke volume (SV), continuous cardiac index (CCI), and stroke volume index (SVI). Additionally, we monitored PPV using an arterial line to ensure adequate administration of fluid during the surgery.

**CASE PRESENTATION**

**Chief complaints**
Old male patient presented to the hospital complaining of severe abdominal pain and a palpable mass in the abdomen.

**History of present illness**
Abdominal distension started at 2 pm and Lt. abdomen was distended severely on arrival to emergency room at 7:50 pm.

**History of past illness**
The patient had been in good health without no-known underlying disease.

**Physical examination**
Abdominal distension began at 2 p.m., and the left side of the abdomen was severely distended upon arrival to the emergency department at 7:50 p.m. His initial vital signs were blood pressure: 142/81 mmHg, heart rate: 112 beats/min, respiratory rate: 20 times/min, and body temperature: 36.3 °C.

**Laboratory examinations**
Initial laboratory tests showed hemoglobin 10.3 g/dL and hematocrit 29.8%.

**Imaging examinations**
Abdominal computed tomography (CT) revealed a 22-cm AML with active bleeding near the left kidney, with a combined pseudoaneurysm (Figure 1).
A case report of a ruptured renal angiolipoma

Jeon WJ et al. A case report of a ruptured renal angiolipoma

Figure 1 A 30-year-old male patient underwent computed tomography to reveal a 22 cm × 13 cm renal angioymolipoma. A: The axial view; B: The coronal view.

FINAL DIAGNOSIS

Left renal AML.

TREATMENT

After considering the patient’s vital signs and laboratory and CT findings, massive active bleeding was suspected, and emergent nephrectomy was scheduled. We expected a large amount of bleeding during surgery and used a non-invasive cardiac monitoring device (CSN-1901, Nihon Kohden, Tokyo, Japan) and PPV to assist evaluation of intravascular volume. These methods are relatively easy and fast to apply compared to invasive cardiac monitoring, which requires placement of a pulmonary catheter.

Upon arrival at the operating room, the patient’s blood pressure was 150/100 mmHg, heart rate was 110 beats/min, and respiratory rate was 20 times/min. Anesthesia was induced through mask ventilation and 100% oxygen with 120 mg intravenous propofol and 50 mg rocuronium. Endotracheal intubation was achieved with a 7.5 endotracheal tube. Anesthesia was maintained with desflurane, nitric oxide, and remifentanil. A right radial arterial cannula was inserted to monitor arterial pressure, and CSM-1901 (Nihon Kohden, Tokyo, Japan) was used to estimate CO, CCI, SV, and SVI. Hemoglobin and hematocrit levels were 10.8 g/dL and 32% at the initial arterial blood gas analysis, respectively.

Laparotomy began with a 15-cm left transverse subcostal incision. Immediately after opening the peritoneum, a huge renal mass with hematoma was observed; the mass was too big to approach all at once. Therefore, part of the mass was dissected, resulting in severe bleeding. A portion of the hematoma was removed, and the surgeon was better able to approach the mass. Nephrectomy was carried out along with removal of the mass. During the surgery, the patient’s CO, CCI, SV, SVI, and PPV were monitored (Figure 2). The patient was estimated to have lost 6000 mL of blood, for which 2950 mL of red blood cells and 953 mL of platelets were transfused. In addition, norepinephrine was administered to maintain proper vital signs. The patient’s final hemoglobin level was 9.7 g/dL, while his hematocrit level was 29%. Prior to extubation, 200 mg of sugammadex was administered for neuromuscular blockade recovery. After extubation, the patient’s vital signs were carefully monitored before transfer to the intensive care unit. Biopsy confirmed the mass to be a ruptured AML that measured 21 cm × 16 cm × 6 cm.

OUTCOME AND FOLLOW-UP

The patient was hospitalized for 9 d and left the hospital without a significant complication.

DISCUSSION

Renal AML is a benign renal neoplasm. Small AMLs are usually asymptomatic and incidentally diagnosed on imaging. However, as the size increases, vascularity increases, resulting in vulnerability to rupture. In one study, the risk of bleeding was 13% with size < 4 cm and 51% with size > 4 cm[4]. Wunderlich syndrome is a spontaneous, non-traumatic renal hemorrhage that arises in the peri-renal space due to various medical conditions, including renal tumors, vascular disease, coagulation
disorders, and idiopathic causes[5]. Urgent contrast-enhanced CT is recommended for diagnosis, and proper management is required because many cases present with hypovolemic shock due to massive hemorrhage. Although proper fluid management is critical, it is extremely difficult to determine the intravascular volume of patients with AML, especially those with active bleeding.

Traditionally, parameters such as blood pressure, heart rate, central venous pressure, and urine output have been used to estimate intravascular volume. However, recent studies support the use of hemodynamic parameters in patients undergoing major invasive surgery because large blood loss and fluid shifting are expected, and this method provides better volume responsiveness compared with traditional parameters[6,7]. The CO is especially important because it is a main determinant of oxygen delivery. CO can be measured invasively (i.e., pulmonary artery and transpulmonary thermodilution), minimally invasively (i.e., esophageal doppler, minimally invasive pulse wave analysis), or non-invasively (i.e., non-invasive pulse wave analysis, pulse wave transit time, thoracic bioimpedance and bioreactance).

PPV was measured using intra-arterial catheter. During controlled mechanical ventilation, the intrathoracic pressure changes between inspiration and expiration, which affects the venous return to the heart and leads to change in SV and blood pressure variations. A PPV > 13% suggests fluid responsiveness and indicates that additional fluid administration might be required[8].

Figure 2 Cardiac parameters were monitored non-invasively using CSN-1901 (Nihon Kohden, Tokyo, Japan) during nephrectomy of a 30-year-old male patients who was diagnosed with ruptured angiomylipoma. Additionally, pulse pressure variation was monitored by intra-arterial catheter. A: Cardiac output; B: Continuous cardiac output index; C: Stroke volume; D: Stroke volume index; E: Pulse pressure variation. CO: Cardiac output; CCI: Continuous cardiac index; SV: Stroke volume; SVI: Stroke volume index; PPV: Pulse pressure variation.
CSM-1901 is a modality based on pulse wave transit time and also utilizes R-waves from the electrocardiogram and pulse waves in the periphery (using a pulse oximeter) along with patient blood pressure and other biometric data to estimate CO and SV. Monitoring traditional parameters using PPV and CO is beneficial to determine intravascular volume[9].

CONCLUSION
Adequate administration of fluid for patients with hemorrhage is a fundamental treatment. In addition to traditional parameters, non-invasive cardiac monitoring and PPV are useful methods to assist evaluation of patient's intravascular volume status and provide a guidance to anesthesiologist for intraoperative management of hypovolemic shock patients.

ACKNOWLEDGEMENTS
The authors thank the Hanyang University E-world center for considerable help during preparation of the manuscript.

FOOTNOTES
Author contributions: All authors including Jeon WJ, Shin WJ, Yoon YJ, Park CW, Shim JH and Cho SY participated in care of the patient, revised this manuscript, and have read and approved the final manuscript.
Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.
Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.
CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).
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S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES


Traumatic giant cell tumor of rib: A case report

Ying-Shian Chen, Hon-We Kao, Hsin-Ya Huang, Tsai-Wang Huang

Abstract

BACKGROUND
Giant cell tumor (GCT) of the anterior rib origin is extremely rare. We report the first case of trauma-induced GCT of the rib.

CASE SUMMARY
A 22-year-old female developed a mass over the right anterior chest wall with pain 3 mo after a falling injury with blunt trauma of the right chest wall. Chest computed tomography (CT) showed a tumor originating from the right 6th rib with bony destruction, and a CT-guided needle biopsy revealed a GCT. We completely resected the tumor with chest wall and performed reconstruction. The pathological diagnosis was GCT of the bone. Twelve months after surgery, no signs of recurrence were observed.

CONCLUSION
GCT of the rib after trauma has not been reported. Meticulous history-taking and image evaluation are essential for the differential diagnosis of unusual chest wall tumors.

Key Words: Chest wall tumor; Giant cell tumor; Trauma; Rib; Bone neoplasm; Case report

Core Tip: We report the first case of trauma-induced giant cell tumor of the anterior rib.
INTRODUCTION

Giant cell tumor (GCT) of the bone accounts for approximately 3%-5% of all primary bone tumors. Occurrence in the ribs, especially the anterior rib, is extremely rare\(^1\). GCT is generally a benign tumor; however, it can progress locally, underscoring the need for a long-term resolution. Risk factors are generally unknown, although Paget disease and Noonan syndrome as risk factors have been reported\(^2,3\). GCT of the rib after trauma has not been reported. Herein, we report the first case of trauma-induced rib GCT with rapid progression in a young female patient. We aim to raise awareness among clinicians about this pathology and possible risk factor of GCT.

CASE PRESENTATION

Chief complaints

A 22-year-old woman, complaining of right chest pain that had persisted for about 3 mo, was referred from the thoracic surgery clinic to the inpatient department.

History of present illness

A 22-year-old female patient complained of right chest pain, which began after a fall injury (3 mo before admission). Chest radiography after the trauma showed no remarkable abnormality (Figure 1A). Despite appropriate analgesia, no sufficient pain relief had been achieved.

History of past illness

The patient had no significant prior medical history.

Personal and family history

The patient had no relevant personal or family history.

Physical examination

A palpable mass was detected over the inframammary line. The mass was 5 cm in size, hard in consistency, tender, and adherent to profound planes (unmovable).

Laboratory examinations

Findings from laboratory examinations were unremarkable.

Imaging examinations

Chest radiography revealed an opacity in the right lower chest wall, with bony destruction (Figure 1B). Computed tomography (CT) indicated a 5-cm tumor in the right anterior chest wall, with destruction of the right 6\(^{\text{th}}\) rib (Figure 2). Whole-body bone scan revealed increased uptake in the 5\(^{\text{th}}\)-7\(^{\text{th}}\) ribs (Figure 3).

FINAL DIAGNOSIS

Histopathology indicated scattered multinucleated giant cells, intermixed with hypercellular spindle to ovoid tumor cells with moderate pleomorphism and extension to the skeletal muscle and bone tissue (Figure 4), consistent with a GCT.

TREATMENT

The patient underwent surgery with excision of the chest wall tumor. Grossly, the tumor was located at the 6\(^{\text{th}}\) rib without invasion to the adjacent structure. The tumor was a soft mass lesion, intermingled with a yellow and black area of 5.5 cm\(^3\) × 5.5 cm\(^2\) × 5 cm\(^3\) in size (Figure 5). The tumor was excised from the 5\(^{\text{th}}\)-7\(^{\text{th}}\) ribs, with a free margin. The defect was reconstructed primarily.
Figure 1 Chest X-ray findings. A: Initial chest film after the trauma revealed no fracture of the rib or mass lesion; B: Chest film at 3 mo after the trauma revealed a 5.1 cm, partially circumscribed mass-like opacity in the right lower chest wall, with adjacent rib destruction.

Figure 2 Chest computed tomographic scan showed a 5-cm tumor at the right anterior chest wall, with destruction of the right 6th rib.

Figure 3 Whole-body bone scan showed increased uptake in the right 5th to 7th ribs.

OUTCOME AND FOLLOW-UP

The surgery was successful, without complications. No signs of recurrence were observed at the 12-mo follow-up.
DISCUSSION

GCT of the bone is a benign but locally aggressive tumor. The meta-epiphyses of the long bones are most affected. Moreover, the most common locations, in decreasing order, are the distal femur, proximal tibia, distal radius, and sacrum[4]. This type of tumor rarely involves the ribs, accounting for only 1% of all cases reported. When located in the rib, most tumors involve the posterior arc of the rib, having an epiphyseal location[5]. Although the histogenesis and pathogenesis of GCT remain incompletely clarified, mononuclear stromal cells are believed to be the neoplastic component of GCT. These cells produce substances that can prevent or regulate osteoclastogenesis, including osteoprotegerin ligands, which function as a secreted natural negative regulator of the receptor activator of nuclear factor-kappa B[6].

For the case presented herein, GCT developed in 3 mo in the anterior ribs following trauma. Although no fracture or bony destruction was initially detected, we assume that the physical damage had induced the stromal cells to produce certain substances. Of note, few cases in the literature have a trauma history. In one such case, GCT developed in the distal ulna 1 year after a scaphoid fracture[7]. Another case had GCT located in the first metacarpal bone following a traumatic event[8]. In the present case, rapid progression with pain symptom mimicked bony malignancy.

The therapeutic strategy for GCT in most patients with potentially completely resectable tumors is surgery. Although GCT of the anterior ribs is rare, the location is relatively excisable, potentially increasing the rate of complete resection which will result in a favorable prognosis. Preoperative tissue evidence from needle biopsy may be helpful but is optional, as surgical resection is indicated regardless of whether the tumor is malignant. Intra-operative pathological consultation may be sufficient to guide the surgical management of each case.
CONCLUSION

Traumatic GCT of the ribs is rare. The manifestation of GCT mimics a malignant bone tumor. Differential diagnoses include metastasis to bone, chondroblastoma, clear cell chondrosarcoma, aneurysmal bone cysts, and lymphoma. Meticulous history-taking, image evaluation, and histological confirmation are essential for the differential diagnosis of unusual chest wall tumors.

FOOTNOTES

Author contributions: Chen YS analyzed the data and wrote the manuscript; Kao HW provided the histopathology description and image; Huang TW designed and directed the study; all authors contributed to the review.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All authors report no relevant conflict of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wu YYJ
L-Editor: A
P-Editor: Wu YYJ

REFERENCES

Analysis of two naval pilots’ ejection injuries: Two case reports

Jia Zeng, Xiao-Peng Liu, Jia-Cheng Yi, Xiang Lu, Dan-Dan Liu, Yan-Qing Jiang, Yan-Bing Liu, Jian-Quan Tian

Abstract

BACKGROUND
Recently, two naval pilots in a two-seat trainer jet were forced to eject urgently due to sudden mechanical failure during night-time training. They were both successfully rescued and sent to the hospital for emergency treatment. In this study, we investigate their ejection injuries and recovery process.

CASE SUMMARY
We analyzed the clinical data of the traumatic condition and recovery process from ejection injuries of two pilots who ejected from a failed trainer jet and survived. After being successfully rescued and sent to the hospital, they were diagnosed with multiple ejection injuries, including eye trauma, limb bone and joint injury, rib and spine injury, and so on. Both cases underwent fluid replacement, acid suppression, nutritional support, hemostasis, bone metabolism improvement, phlegm elimination, psychological measurement, blood circulation promotion and detumescence, physical therapy, and external fixation with braces for 1 mo before being discharged from hospital. They then recuperated in a sanatorium for 2 mo, and the related laboratory tests and supplementary examinations show that they recovered from all the above injuries. After successfully passing the psychological test and physical examination, they returned to flight duty 3 mo after ejection.

CONCLUSION
The causes and conditions of ejection injury in the pilots were very complex. Although they finally recovered quickly and were released, it also serves as a reminder that attention should be paid to pilots’ ejection and parachute training in order to significantly reduce ejection injury and improve the ejection success rate. In addition, air defense support personnel should strengthen search and rescue...
and on-site emergency measures, and locate and rescue pilots in distress as early as possible to reduce subsequent injuries.

**Key Words:** Aerospace medicine; Pilots; Aviation accidents; Wounds and injuries; Case report

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**Core Tip:** The ejection injuries to pilots are usually very complex. We analyzed two pilots’ traumatic condition and recovery process after they were ejected from a failed trainer and survived. After being successfully rescued, they were diagnosed with multiple ejection injuries and underwent a series of treatments for 1 mo. They then recuperated for 2 mo, and the related tests and examinations show that they recovered from injuries. After passing the psychological test and physical examination, they successfully returned to flight duty. Attention should be paid to pilots’ ejection training in order to reduce ejection injury and improve the ejection success rate. In addition, aviation rescuers should strengthen search techniques to locate and rescue pilots in distress as early as possible to reduce injuries.

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**Citation:** Zeng J, Liu XP, Yi JC, Lu X, Liu DD, Jiang YQ, Liu YB, Tian JQ. Analysis of two naval pilots’ ejection injuries: Two case reports. *World J Clin Cases* 2022; 10(24): 8667-8672

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i24/8667.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i24.8667

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**INTRODUCTION**

Ejection is an important way for pilots to escape planes in case of emergency, but the incidence of injury accompanying ejection escape is also very high[1-3]. As the conditions of ejection injuries are complex and diverse, it is very important to study ejection injuries and take targeted first-aid measures to save the lives of pilots in distress[4].

Recently, two naval pilots in a two-seat trainer jet were forced to eject urgently due to sudden mechanical failure during night-time training. The flight speed during the ejection was about 700 km/h, which was within the flight envelope. The ejection mode was rocket-assisted through-canopy ejection. At the moment of ejection, they experienced transient loss of consciousness. They were both successfully rescued and sent to the hospital for emergency treatment. After being diagnosed with multiple ejection injuries, they recuperated in a sanatorium for 2 mo, and the related laboratory tests and supplementary examinations show that they recovered from their injuries. After successfully passing the psychological test and physical examination, they returned to flight duty 3 mo after ejection. Their injury conditions and recovery process are presented below.

---

**CASE PRESENTATION**

**Chief complaints**

**Case 1:** A male flight cadet in the front cabin, 20-years-old, with total flight time of 300 h, suffered from multiple injuries to the whole body 2 h after ejection.

**Case 2:** A male flight instructor in the rear cabin, 40-years-old, with total flight time of 1700 h (including 280 h in the current aircraft model), suffered from multiple injuries to the whole body 11 h after ejection.

**History of present illness**

**Case 1:** Due to mechanical failure, the pilot ejected and parachuted from the front cabin of the trainer jet with transient loss of consciousness. He had recovered consciousness by the time he landed. He experienced chest pain, back pain and other body pains, and limited movement of the right ankle. Two hours after ejection, he was found by the villagers and sent to the local hospital by ambulance.

**Case 2:** Due to mechanical failure, the pilot ejected and parachuted from the rear cabin of the trainer jet with transient loss of consciousness. He regained consciousness after landing. He felt pain all over his body and limited movement of the left knee. Eleven hours after ejection, he was found and sent to the local hospital by ambulance.
History of past illness
No other abnormal health conditions were reported in both cases.

Personal and family history
Both cases had no specific history of genetic diseases.

Physical examination
Case 1: The pilot was found with blueness and bilateral swelling on the eyelids; a splinter hemorrhage in the right conjunctiva, and swelling and percussion pain (+) in the neck, back, and waist; tenderness (+) in the T3-T5 and T8 vertebral spinous process; slightly limited thoracic vertebral extension; tenderness (+) and percussion pain (+) in the right hypochondriac region; swelling in the right ankle, tenderness (+) in the right lateral ankle and posterior ankle, slightly limited varus, and right lower limb muscle strength 4 +; and multiple skin abrasions on the back, waist, and extremities.

Case 2: The pilot was found with bilateral edema of the eyelids and a small splinter hemorrhage in the right conjunctiva; multiple abrasions on the face, bilateral forearm and legs, and swelling and bruising on the posterior-lateral left thigh; cyanosis of the skin, and swelling, tenderness (+), and immobility around the left knee joint.

Laboratory examinations
Case 1: Aspartate aminotransferase 53 U/L, procalcitonin 0.51 ng/mL, indirect bilirubin 22.65 μmol/L, creatine kinase 175 IU/L, C-reactive protein (CRP) 8.1 mg/L, phosphocreatine kinase isoenzyme 33 U/L, and lactate dehydrogenase 360 U/L.

Case 2: Creatine kinase 1133 IU/L, creatinine 101 μmol/L, CRP 22.5 mg/L, phosphocreatine kinase isoenzyme 22 U/L, and lactate dehydrogenase 277 U/L.

Imaging examinations
Case 1: Magnetic resonance imaging (MRI) showed: C3/4 and C4/5 intervertebral disc herniation; mild compression fractures of T3-T5 and T8 vertebral bodies; bone marrow edema of T1-T8 vertebral bodies and L5/S1 intervertebral disc herniation; laceration of anterior talofibular ligament of the right ankle; local Grade 1 injury of Achilles tendon of right ankle; bone marrow edema of right calcaneus; and soft tissue edema around right ankle. Chest computed tomography (CT) showed incomplete fractures of multiple right ribs (anterior ribs 5-9) (Figure 1A-D).

Case 2: MRI showed: Lumbar disc herniation of L3/4; thoracic T3 vertebral hemangioma.

FINAL DIAGNOSIS
Case 1
Ocular trauma, subconjunctival hemorrhage (right); cervical disc herniation (C3/4, C4/5); multiple thoracic vertebral compression fractures (T3-T5, T8); incomplete fracture of multiple right ribs; Achilles tendon injury (right, Grade 1); laceration of anterior talofibular ligament of ankle (right); calcaneal contusion (right); and soft tissue injury in right ankle and lower back.

Case 2
Ocular trauma, subconjunctival hemorrhage (right eye); left medial femoral condylar bone contusion with bone marrow edema; multiple injuries to posterior tendons and ligaments of left thigh; acute kidney injury; thoracic T3 vertebral hemangioma; and lumbar disc herniation (L3/4).

TREATMENT
After admission, the two injured pilots were treated with fluid replacement, acid suppression, nutritional support, hemostasis, bone metabolism improvement, phlegm elimination, psychological measurement, blood circulation promotion and detumescence, physical therapy, and external fixation with braces for 1 mo before being discharged from hospital.

OUTCOME AND FOLLOW-UP
After discharge, they recuperated in a sanatorium for 2 mo, the related laboratory tests and supple-
mentary examinations show that they recovered from all injuries. Psychological assessment: Healthy. Physical fitness test: Qualified. They were released 3 mo after the ejection (Figure 1E-H).

DISCUSSION

Congestive bilateral eyelid and right eyeball conjunctiva were potentially caused by the effects of continuous negative gravity (-G) conditions on visual function[5]. The analysis showed that both pilots were suspended upward when the danger occurred. At this time, -G caused blood to flow to the head, which led to the congestion of bulbar conjunctiva, increased the secretion of lacrimal glands, and caused eyelid edema and blurred vision. Continuous -G can also cause: (1) Changes in visual function; increased secretion of the lacrimal glands can lead to blurred vision; edema of the lower eyelid, shifting upward to cover the pupil and cause difficulty in opening the eyes, can lead to the temporary loss of vision; and conjunctiva rupture and hemorrhage, causing blood-stained tears to accumulate in the conjunctival sac, results in the redness of the visual field. The congested lower eyelid shifted upward to cover the pupil, and strong light irradiation led to the redness of visual field. Retinal circulation stagnation and hypoxia, and the lower eyelid covering the pupil, led to the loss of central vision; edema of the orbital tissue and disorder of the coordinated movement of the extraocular muscles led to diplopia; (2) Congestion in the reflux area of the superior vena cava can result in the congestion and edema of the neck and face, as well as subcutaneous hemorrhage points; (3) With the diaphragm in an upward position, ventilation blood flow imbalance can lead to dyspnea; (4) Increased intracranial pressure can lead to headache and distension of the head, as well as increased blood pressure; and (5) Increased carotid sinus pressure can lead to an abnormal heart rate.

Temporary loss of consciousness, spinal injury, head and neck injury and limb injury were likely due to the overload value during ejection, which may have reached about 20 G, with a high growth rate of G value and short action time. The ejection through the canopy increased the G value and G growth rate significantly. After ejection from the aircraft and before the parachute opens, the person-chair system or human body may rotate under the impact of the high-speed airflow. The inertial centrifugal force may cause equipment, such as oxygen masks, gloves, flight boots, and pistols to fall off, and the headband of the mask may injure the neck[4-6]. The high-speed airflow may also cause hypoxia and frostbite in pilots[3,4]. Both pilots experienced the transient loss of consciousness during ejection, and only recovered their consciousness during parachuting. The cadet in the front cabin had multiple thoracic vertebral compression and rib fractures, and a cervical disc herniation, while the instructor in the rear cabin had a cervical and lumbar disc herniation; it is considered that they were already displaced at the time of ejection. The mask and helmet caused minor injuries to the head and neck, and the cadet in the front cabin incurred neck strangulation and limb injury due to the displacement and collision of the limbs and loss of consciousness during ejection.

Parachute-opening injury is more common at the exerting parts of harness system, such as the scapula, chest and waist, and perineum, which can cause sternum, rib, spine, and limb fracture and dislocation, as well as visceral injuries[7]. The pilots presented multiple fractures to the right ribs, which was considered to have been caused by the parachutes opening. Meanwhile, parachuting is not excluded from being the cause of spinal injury in both patients.

Sprains and contusions to the lower limb joints and ligaments are mostly caused by landing. The cadet in the front cabin suffered from a right Achilles tendon injury; laceration of the anterior talofibular ligament of the right ankle; right calcaneal bone contusion; and soft tissue injury in the right ankle, back, and waist. The instructor in the back cabin suffered from left medial femoral condylar bone contusion with bone marrow edema, and multiple injuries to the posterior tendons and ligaments of the left thigh[8]. Moreover, the incident occurred in a jungle mountain area at night, so the poor visibility, more numerous obstacles, and improper landing posture could have aggravated the injuries. Both cases were found with abnormal enzyme labeling and elevated CRP at the time of admission, which were caused by muscle injury and systemic inflammatory reaction after injury. The instructor in the back cabin also showed abnormal creatinine and slightly increased urinary microproteins, which was related to his landing on the top of a mountain, longer rescue time, prolonged lack of water, and insufficient strength. The laboratory indexes all improved after active treatment.

Aeromedical concerns

The causes of ejection injury in these cases are complex. The two pilots carried out the ejection properly. Fortunately, they did not suffer from any visceral or fatal disability injuries, and recovered quickly and were released. However, it also serves as a reminder that attention should be paid to pilots’ ejection and parachute training. Before ejection, the flight parameters should be controlled within the ejection envelope (safe flying height and descent rate) as much as possible. The perfect mastery of ejection skills by pilots may contribute to significantly reduced ejection injury and improved ejection success rate[9, 10]. Meanwhile, air defense support personnel should strengthen search and rescue and on-site emergency measures, and locate and rescue pilots in distress as quickly possible to reduce subsequent injuries[11].
CONCLUSION

Attention should be paid to pilots’ ejection and parachute training in order to significantly reduce ejection injury and improve the ejection success rate. In addition, air defense support personnel should strengthen search and rescue and on-site emergency measures, and locate and rescue pilots in distress quickly to reduce subsequent injuries.

Figure 1 Magnetic resonance imaging contrast in case 1 before and after treatment. A and B: Magnetic resonance imaging (MRI) of thoracic vertebra in case 1 before treatment; C and D: MRI of thoracic vertebra in case 1 after treatment; E and F: MRI of ankle joint in case 1 before treatment; G and H: MRI of ankle joint in case 1 after treatment.
Zeng J et al. Ejection injuries in two navy pilots

FOOTNOTES

Author contributions: Zeng J and Liu XP contributed equally to this work; Zeng J and Tian JQ designed the study; Zeng J, Yi JC, Liu DD, Jiang YQ, Lu X, and Liu YB collected and analyzed the clinical data; Zeng J and Yi JC wrote the manuscript; Tian JQ revised the manuscript.

Supported by Key Projects of Medical Service Scientific Research of the Navy Medical Center, No. 20M2302.

Informed consent statement: We obtained consent from all patients or their relatives for the publication of this report.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Yan JP
L-Editor: Filipodia
P-Editor: Yan JP

REFERENCES

4 Dikshit MB. To Err is Human Case Reports of Two Military Aircraft Accidents: Possible mechanisms of human failure. Sultan Qaboos Univ Med J 2010; 10: 120-125 [PMID: 21509093]
Beware of the DeBakey type I aortic dissection hidden by ischemic stroke: Two case reports

Su-Qin Chen, Wei-Liang Luo, Wu Liu, Li-Zhi Wang

Abstract

BACKGROUND
DeBakey type I aortic dissection is one of the rare etiologies of ischemic stroke. It is critical to identify arterial dissection before intravenous thrombolysis; otherwise, fatal hemorrhage may occur.

CASE SUMMARY
In this report, we described 2 painless DeBakey type I aortic dissection cases with initial symptoms similar to ischemic stroke. Sudden onset of conscious disturbance and limb weakness within minutes occurred in both cases. Hypotension was found in both cases. Thoracoabdominal computed tomography angiography was urgently performed due to unknown reason hypotension, and DeBakey type I aortic dissection was confirmed. Intravenous thrombolysis was avoided because of timely diagnosis; however, they both eventually died of ruptured aortic dissection.

CONCLUSION
Aortic dissection should always be excluded in ischemic stroke patients with unexplained hypotension or shock symptoms before intravenous thrombolytic therapy.

Key Words: Ischemic stroke; Aortic dissection; Diagnosis; Case report
Core Tip: Aortic dissection should always be excluded in ischemic patients with unexplained hypotension or shock symptoms before intravenous thrombolytic therapy. These two painless DeBakey Type I aortic dissection cases with initial symptoms similar to ischemic stroke intravenous thrombolysis was avoided because of timely diagnosis.

URL: https://www.wjgnet.com/2307-8960/full/v10/i24/8673.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i24.8673

INTRODUCTION
Acute ischemic stroke (AIS) is the leading cause of death and disability in the world. It is defined as the sudden loss of blood flow to an area of the brain, resulting in a corresponding loss of neurologic function. In order to rescue more penumbra tissue, vascular recanalization treatment, such as intravenous thrombolysis or endovascular clot retrieval, should be carried out as soon as possible because the recanalization time is directly related to the outcomes[1]. Although intravenous thrombolysis is widely used, carefully excluding patients with contraindications of thrombolytic therapy is critical. Aortic dissection is the absolute contraindication of thrombolytic therapy, and it is an uncommon, life-threatening cause of ischemic stroke. Typical aortic dissection presents with tearing chest or back pain, but painless aortic dissection with only focal neurological deficits can be a challenge for emergency physicians, and inadvertently treating this situation with thrombolytic agents may threaten the patient’s life.

In this report, we describe 2 painless DeBakey type I aortic dissection patients presenting initial symptoms similar to ischemic stroke who were eligible for thrombolytic treatment. We report these cases with the aim to emphasize the importance of ruling out aortic dissection before fibrinolytic treatment in AIS patients.

CASE PRESENTATION
Chief complaints
Case 1: A 73-year-old Chinese man was brought to the emergency room by the family with the complaint of sudden onset of altered consciousness and right-limb weakness for 1 h.
Case 2: A 68-year-old male suddenly lost consciousness one and half hour ago while standing up from the squat position.

History of present illness
Case 1: Symptoms of right-limb weakness, altered consciousness, and urinary/bowel incontinence occurred within ten seconds to minutes observed by the family 1 h ago while he was cooking. No nausea or vomiting was observed during the clinical course.
Case 2: Symptoms occurred concurrent with the postural change. After arriving at the emergency room, the patient became conscious and complained of neither chest or back pain, nor nausea or vomiting. He presented with slight dysarthria and slow response.

History of past illness
Case 1: The patient had intermittent gout attacks for 3 years.
Case 2: The patient was diagnosed with “cerebral infarction” 21 years ago for the sudden onset of left limb weakness. He underwent decompressive craniectomy for “cerebral hemorrhage” 19 years ago. He had "subarachnoid hemorrhage" 12 years ago and recovered after conservative treatment. The patient was independent for daily activities and could walk upstairs and downstairs without issues before this attack.

Personal and family history
Case 1: The family denied any family history of similar medical conditions or genetic disease.
Case 2: He had a drinking history of more than 30 years but had quit drinking for more than 10 years. He smoked for more than 30 years but quit smoking 10 years ago. The patient denied any family history
of similar medical conditions or genetic disease.

**Physical examination**

**Case 1:** On physical examination, the patient had a pale face and wet and cold limbs. The vital signs were as follows: Body temperature, 36.8 °C; blood pressure (BP), 98/58 mmHg (right arm), 101/60 mmHg (left arm); heart rate, 56 beats per min; respiratory rate, 22 breaths per min. There was no murmur in the heart valve auscultation area. Nervous system condition: Blurred consciousness with Glasgow Coma Scale of 10 point, passive posture, Broca’s aphasia, grade II muscle strength of the right limb, normal muscle strength of the left limb, and positive Babinski sign of right lower limb.

**Case 2:** Low BP (84/68 mmHg) was detected at the emergency room, but was found to be normal at the neurology department. The vital signs at neurology department were as follows: Body temperature 36.0 °C; BP, 121/74 mmHg (right arm); 110/60 mmHg (left arm); heart rate 89 beats per min; respiratory rate 15 breaths per min. Furthermore, the patient had obvious cyanosis. The muscle strength of the four limbs had decreased slightly with grading V-.

**Laboratory examinations**

**Case 1:** Complete blood count was normal. Blood biochemistry indicates renal insufficiency (creatinine, 201 μmol/L; urea nitrogen, 11 mmol/L). D-dimer was more than 16 μg/mL.

**Case 2:** D-dimer was elevated (1.9 μg/mL). Blood gas analysis indicated low blood oxygen (pressure of O₂, 9.47 kPa). Complete blood count was normal.

**Imaging examinations**

**Case 1:** Computed tomography (CT) of the brain did not find any low-density focus, which indicated that the patient was eligible for thrombolytic treatment. Doppler ultrasound of the carotid artery was applied in an attempt to determine the possible cause of the unexplained hypotension, and it found both right common carotid and right internal carotid artery dissection (Figure 1A). Bedside chest X-ray indicated widening of the right mediastinum (Figure 1B). Therefore, thoracic and abdominal CT angiography (CTA) was urgently performed, and DeBakey type I aortic dissection was confirmed (Figure 1C and D).

**Case 2:** The chest X-ray did not reveal mediastinum widening. A cranial CT scan showed multiple chronic brain infarctions (Figure 2A). Considering the high risk of bleeding in this patient, the family refused intravenous thrombolysis. Due to unexplained cyanosis and sweating limbs, a thoracoabdominal CT scan was performed in an attempt to determine the underlying causes. The CTA enabled a definite diagnosis of DeBakey type I aortic dissection (Figure 2B and C).

**FINAL DIAGNOSES**

**Case 1:** Combined with the patient’s clinical history and imaging findings, the final diagnosis was DeBakey type I aortic dissection complicated with cerebral infarction. Chronic renal insufficiency was the secondary diagnosis.

**Case 2:** Combined with the patient’s clinical history and imaging findings, the final diagnosis was DeBakey Type I aortic dissection complicated with cerebral infarction. Chronic cerebral infarction was the secondary diagnosis.

**TREATMENT**

**Case 1:** Since our hospital was unable to perform the open surgery to repair the damaged aorta, we recommended the patient be transferred to another hospital. Carefully monitoring vital signs, controlling BP, and avoiding excessive exertion were implemented before referral.

**Case 2:** We carefully monitored the patient’s vital signs, controlled BP, and gave appropriate sedation. We suggested the patient be transferred to another hospital for surgical treatment.

**OUTCOME AND FOLLOW-UP**

**Case 1:** On the 2nd day of admission, the patient suddenly died due to rupture of the arterial dissection before the transfer.
Chen SQ et al. Aortic dissection presented as ischemic stroke

Figure 1 Imaging examination of Case 1. A: Doppler ultrasound of the common carotid artery indicated artery dissection; B: Chest X-ray showed mediastinum widening; C: Sagittal vascular reconstruction imaging; D: Transverse sectional image of the aorta showed the artery dissection (arrows).

Figure 2 Imaging examination of Case 2. A: Cranial computed tomography (CT) scan showed multiple softened foci and old infarcted foci in the brain; B and C: Sagittal and transverse section of the chest, respectively. The CT angiography showed the aortic dissection.

Case 2: The patient died 10 h after admission when his family members were discussing whether to transfer him to a different hospital for surgical treatment.

DISCUSSION

Acute aortic dissection (AAD) is characterized by the rapid development of an intimal flap. This is caused by blood flowing into the media and forcing the intima and the adventitia apart, which leads to life-threatening complications and death, particularly when the ascending aorta is involved[2]. According to the location of the dissection and/or origin of the intimal tear and the extent of the dissection, AAD can be classified into Stanford type A (or DeBakey type I and type II) and Stanford type B (or DeBakey type IIIa and type IIIb). Stanford type A aortic dissections involve the ascending aorta and usually require swift, open surgical repair, whereas Stanford type B dissections involve the descending but not the ascending aorta and are conventionally treated by endovascular repair and/or medical therapy[2]. AAD is an uncommon but life-threatening disease with a reported incidence of 3–5 cases per 100000 people per year[3], a figure which may rise to even as high as 35 cases per 100000 people per year at the age of 65–75-years-old[4]. About 20% of the untreated patients with DeBakey type I aortic dissection died immediately, whilst a further 1%-2% of the survivors died with every hour of delayed treatment[5].

Stroke is one of the most serious complications of DeBakey type I AAD, and the incidence of DeBakey type I arterial dissection complicated with stroke is about 6%[6] to 10%[7]. Arterial dissection represents 5.7% of first-ever ischemic strokes of unusual cause in a clinical series[8]. Arterial dissection presented with stroke symptoms and without typical chest or back pain can lead to a delayed diagnosis of dissection and that can significantly increase the mortality. Furthermore, thrombolysis treatment can result in 3-5 fold higher probability of fatalities than non-thrombolysis treatment of patients[9]. Therefore, urgently identifying the presence of arterial dissection in stroke patients is critical.

While aortic dissection can involve both of the carotid arteries, right hemisphere involvement is more commonly seen in previous reports[7]. The frequency of chest/back pain is much lower in AAD patients combined with stroke than those without stroke[7]. Altered consciousness, which may be either due to the sudden drop of BP after arterial dissection or damage of the brain, can lead to delayed reporting of
chest/back pain. SBP difference greater than 20 mmHg between the two upper limbs is one of the characteristics of AAD, but in our case series, none of them had such manifestations. Furthermore, pulse deficits are present in about 20%–30% of ADD cases which emphasizes the importance of serial physical examinations that can substantially contribute to the correct diagnosis. Transient or persistent low BP or shock symptoms should always be taken seriously in ischemic stroke patients because most ischemic stroke patients usually have higher BP\[7\].

D-dimer is an important predictive value in the diagnosis of AAD, and D-dimer values less than 0.5 μg/mL can be used to rule out AAD\[10\]. However, D-dimer elevation is also common in acute stroke, deep venous thrombosis and pulmonary embolism, particularly in cardioembolism\[11\]. D-dimer elevation has poor specificity in the diagnosis of aortic dissection, but is helpful to exclude aortic dissection when D-dimer is negative.

The contrast-enhanced CT scan is a reliable method for the definite diagnosis of AAD. In addition to enhanced CT scan, other auxiliary examinations, such as carotid ultrasound and chest X-ray, can also provide reference values for AAD diagnosis. Chest X-ray can be considered as part of the acute screening protocols in AIS patients with special enlarged mediastinal shadow in AAD. A common or internal carotid artery dissection can easily be investigated by ultrasonography, which can be regarded as a helpful, complementary tool for the current diagnostic workup\[12\].

Arterial dissection is a life-threatening emergency which needs urgent surgery or endovascular intervention. It is highly recommended to keep the SBP < 120 mmHg with intravenous β-blockers or vasodilators and careful management of any conditions that can increase thoraco-abdominal pressure is required to prevent the complication of aortic rupture prior to surgery or endovascular intervention.

**CONCLUSION**

In conclusion, when AIS patients developed a rapid peak of neurological symptoms, unexplained hypotension, or shock symptoms, arterial dissection as a differential diagnosis should always be excluded before intravenous thrombolysis. Serial monitoring, such as checking the differences in SBP between the two arms and peripheral arterial pulsation are important for diagnosis of arterial dissection. An abnormal carotid ultrasound finding and mediastinal widening on chest radiograph may also be helpful in identifying AAD. The elevation of D-dimer has no specificity value in diagnosing arterial dissection, but its negative value has high specificity in excluding AAD. For AIS patients who are suspected of arterial dissection, enhanced CTA examination is needed urgently to confirmed the diagnosis. To avoid arterial rupture, close monitoring of vital signs, ensuring proper bed rest, and the treatment of coughing and constipation are very important.

**FOOTNOTES**

**Author contributions:** Chen SQ and Luo WL contributed to manuscript writing and editing; Luo WL contributed to conceptualization and supervision; Liu W and Wang LZ contributed to data collection and data analysis; All authors have read and approved the final manuscript.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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**S-Editor:** Fan JR

**L-Editor:** Filipodia

**P-Editor:** Fan JR
REFERENCES


Unilateral lichen planus with Blaschko line distribution: A case report

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Specialty type: Dermatology
Provenance and peer review: Unsolicited article; Externally peer reviewed.
Peer-review model: Single blind
Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Park HK, South Korea; Vyshka G, Albania; Zhang Y, China
Received: February 14, 2022
Peer-review started: February 14, 2022
First decision: March 24, 2022
Revised: April 3, 2022
Accepted: July 25, 2022
Article in press: July 25, 2022
Published online: August 26, 2022

BACKGROUND
Lichen planus (LP) with distribution of lesions along Blaschko’s lines is a rare entity, accounting for 0.24%-0.62% of all patients. Unilateral distribution of lesions in arm, leg, trunk, and waist is even less common. Approximately 10% of patients with LP manifest nail lesions.

CASE SUMMARY
A 20-year-old woman presented to our department with polygonal, purpuric, flat-topped papules over the right arm, right leg, and right side of trunk and waist for the last 5 mo. The patient initially developed nail deformation in the left middle finger with no obvious cause, followed by development of blue-purple and red maculopapular rash with pruritus. During the disease course, the skin lesions aggravated and spread to several segments due to scratching. The lesions showed unilateral distribution along the Blaschko’s lines. The diagnosis of LP along Blaschko’s lines was established based on dermoscopy and skin biopsy. Her cutaneous lesions considerably improved after 4-wk treatment with intramuscular glucocorticoid, oral acitretin, topical glucocorticoid, and retinoids.

CONCLUSION
Cases of LP involving multiple segments of the body along the Blaschko’s lines with nail damage are rare.

Key Words: Lichen planus; Blaschko’ lines; Lichen planus involving nails; Case report
Core Tip: Lichen planus (LP) with lesion distribution along the Blaschko’s lines can be differentiated from other skin lesions with linear distribution by dermoscopy and pathological biopsy. The isotopic response can occur in patients with LP, which may be an important cause for rapid spread of lesions and involvement of multiple segments. Therefore, early diagnosis and treatment are of great significance. Treatment strategy should be individualized based on the lesion characteristics and patient acceptance. Our patient showed considerable improvement of cutaneous lesions after 4-wk treatment with intramuscular glucocorticoid, oral acitretin, topical glucocorticoid and retinoids.

INTRODUCTION
Although cases of lichen planus (LP) are not uncommon, LP with lesion distribution along the Blaschko’s lines is a rare entity, accounting for only 0.24%-0.62% of all patients with LP [1]. Cases with unilateral involvement of upper and lower limbs, chest, back, and waist are even rarer. Approximately 10% of patients with LP have nail lesions [2]. We report a rare case of LP with unilateral distribution of cutaneous lesions along the Blaschko’s lines along with nail lesions. Our experience with this case may provide insights into this rare disease and facilitate timely diagnosis and treatment of this disease.

CASE PRESENTATION
Chief complaints
On September 24, 2021, a 20-year-old woman presented to our department with polygonal, purpuric, flat-topped papules over her right arm, right leg, and right side of trunk and waist since the last 5 mo.

History of present illness
In January 2021, the patient noted asymptomatic deformation of her left middle finger nail with no obvious cause along with splitting of the distal nail plate. In April 2021, due to exposure to cherry blossom, she developed red miliary size papules on the inner aspect of right upper arm with severe itching, and was diagnosed with allergic dermatitis at a local hospital. Her symptoms improved after treatment with loratadine and topical compound dexamethasone acetate cream. In May 2021, she had symptoms of hyperhidrosis followed by development of a red polygonal flat papule (size: 5 mm) with pruritus in her right lower limb. Her symptoms were not relieved after topical application of desonide cream. One week later, a similar lesion appeared on the right side of waist. In June, her symptoms were alleviated, and she had black discoloration of some lesions. In July, the patient had recurrence of pruritus on the same site with no obvious triggering factor. After scratching, the eruption on the right upper extremity and right lower extremity spread to distal sites along the longitudinal axis, which brought the patient to our department.

History of past illness
Her past history was unremarkable.

Personal and family history
There was no family history of similar disease.

Physical examination
Systemic examination revealed no obvious abnormalities. Cutaneous examination showed violaceous, erythematous macules and maculopapules sized 1-5 mm on the right upper and lower limbs and on the right side of chest, back and waist. Some of the lesions had coalesced into flaky plaques with no obvious scale formation. The lesions were distributed unilaterally without crossing the midline, along the Blaschko’s lines (Figure 1A-C and E). There was no abnormality in oral mucosa. Splitting in the distal plate of the left middle finger was present and nail pit was also seen (Figure 2).

Laboratory examinations
Due to the financial constraints of the patient, relevant laboratory examinations were not conducted.
Dong S et al. Unilateral lichen planus along Blaschko’s line

Figure 1 Clinical photographs. A: Violaceous, brownish, polygonal papules on the right abdomen along the Blaschko’s lines; B: Violaceous, brownish papules and plaques distributed along the Blaschko’s lines on the right back and extended to the upper extremity. C: Before treatment, violaceous and red maculae with a size of 1-5 mm were seen on the right lower limb, and maculae papules were partially coalesced into patchy maculae linearly distributed; E: Before treatment, violaceous and red maculae were seen on the right upper limb; D and F: After treatment, the old lesions disappear or only pigmentation patches remain.

**Imaging examinations**

Dermoscopy examination showed linear and punctate blood vessels in the lesions. The vascular structure was radially arranged, and white reticular stripes were seen (Figure 3A). Histopathological examination showed reticular hyperkeratosis of the stratum corneum, wedge-shaped thickening of the granular layer, irregular thickening of spinous layer, basal cell vacuolization and liquefaction, compact bandlike lymphocytic infiltration in superficial dermis, and sporadic infiltration of chromatophilic cells. These were typical features of LP (Figure 4).

**FINAL DIAGNOSIS**

LP along the lines of Blaschko’s.

**TREATMENT**

The patient was prescribed compound betamethasone (glucocorticoid) 5 mg by intramuscular injection; capsule acitretin 10 mg (oral) once daily; topical fluticasone propionate (glucocorticoid) cream, twice
Figure 2 Nail damage. Arrow: Distal deck splitting; Triangle: nail pits.

Figure 3 Dermoscopic photographs (50×). A: Before treatment, linear and punctured vessels were seen under dermoscopy. The vascular structure was arranged radially with obvious white stripes; B: After treatment, the vascular structure disappeared, leaving blue-gray spots and faint white reticular stripes.

Figure 4 Skin histopathology (hematoxylin-eosin staining, 100×). Histopathological examination showed reticular hyperkeratosis of the stratum corneum, wedge-shaped thickening of granular layer, irregular thickening of spinous layer, basal cell vacuolization and liquefaction, compact bandlike lymphocytic infiltration in superficial dermis, sporadic infiltration of chromatophilic cells, which shows typical features of lichen planus.

daily; and topical adapalene gel, once daily. The patient’s symptoms showed considerable improvement after 4-wk treatment with the above regime.
OUTCOME AND FOLLOW-UP

Follow-up examination after 4 wk revealed no new cutaneous lesion, while the old cutaneous lesions were resolved or had become pigmented patches with no pruritus (Figure 1D and F). Dermoscopy revealed disappearance of the vascular structure with residual blue-gray spots and faint white reticula stripes (Figure 3B). There was no significant improvement in nail deformation. At 16 wk, the cutaneous lesions had disappeared, but there was still no significant improvement in nail damage.

DISCUSSION

The concept of Blaschko’s lines was first proposed by Alfred Blaschko in 1901. It does not follow the distribution of blood vessels, lymph nodes, or nerves, but rather reflects the direction of spread of cell cloning and differentiation during embryonic development[3]. It is believed that LP along the Blaschko’s lines is found in 0.24%-0.62% of all LP patients[1], and nail LP affects approximately 10% of all patients with cutaneous LP[2]. In the published literature, cases of LP with unilateral distribution of lesions along the Blaschko’s lines mostly showed involvement of the trunk and limbs[1,4-6]. Our patient had extensive lesions involving the right upper and lower limb and right side of chest, back and waist.

The development of Koebner phenomenon in LP is well documented. It refers to the appearance of new skin lesions on areas of cutaneous injury or trauma in otherwise healthy skin[7,8]. In the present case, the cutaneous lesions may have resulted from allergic dermatitis or due to the spread of lesion caused by scratching. Patients with LP should be advised to avoid trauma and seek medical treatment as early as possible to avert further aggravation of symptoms.

The diagnosis of LP relies on the typical morphology of lesions at the affected site with histopathological correlation[9,10]. The histological features of LP with lesion distribution along Blaschko’s lines is identical to those of generalized LP[11]. Laboratory investigations can help rule out other systemic diseases or infectious diseases. Unfortunately, our patient did not undergo laboratory investigations due to financial constraints. The differential diagnoses in the present case included inflammatory linear verrucous epidermal nevus (ILVEN), lichen striatus, and linear porokeratosis[3]. ILVEN typically occurs in children aged < 5 years and generally involves the legs with intense pruritus. Lichen striatus predominantly occurs in children below the age of 15 years. It typically manifests as asymptomatic linear papules arranged in the form of band with slight scaling and hypopigmentation over proximal parts of limbs with spontaneous resolution in 3-6 mo[12]. Linear porokeratosis typically occurs in infants[13], and it can be type I lichen striatus or an isotopic response triggered by trauma. Differential diagnosis can be done based on the history, characteristics of cutaneous lesions, and findings of dermoscopy and histopathological examination. In addition, our case was consistent with type I nail LP, i.e., typical cutaneous lesion with nail damage[14]. After the diagnosis of LP, the diagnosis of nail LP is straightforward.

The majority of cases of cutaneous LP show spontaneous resolution within 1 or 2 years[15]. However, in a study, LP patients rated their disease on the Dermatology Life Quality Index as equivalent to that of psoriasis. The resulting decrease in the quality of life places increased emphasis on the need for effective, lasting treatments for LP[16]. The first-line treatment for cutaneous LP includes topical steroids, intralesional injection of triamcinolone acetonide, systemic corticosteroid therapy (oral or intramuscular injection), oral acitretin or isotretinoin[10,17]. Intramuscular corticosteroids show similar efficacy and improved safety in comparison to oral steroids, since the former allows for stable release of corticosteroids over a relatively long time. Intramuscular corticosteroids are considered the most reliable treatment for refractory LP with an overall success rate of 79%. Besides, topical retinoids also have a good therapeutic effect[18]. Similar cases reported previously were predominantly treated with topical steroids or oral prednisone[1,4-6]. Considering the advantages of intramuscular injection and the patient’s condition (extensive cutaneous lesions and failure of topical injection), we opted for the following treatment regime and achieved good outcome: compound betamethasone (glucocorticoid) 5 mg (intramuscular injection); oral acitretin 10 mg once daily; topical fluticasone propionate cream, twice daily; and topical adapalene gel, once daily.

Compared with the treatment of cutaneous LP, treatment of nail LP is challenging due to limited treatment options and the tendency for frequent relapse[19]. Systemic application of glucocorticoids is more effective than topical agents alone, thus systemic administration should be used as early as possible for the treatment of nail LP[2,20]. The nail condition of our patient showed no significant improvement after treatment. A previous case report described considerable improvement in nail lesions after treatment with topical methoxypсорalen and UV A for 4 mo[21]. We could not implement this treatment because of the study schedule of the patient. The patient is currently being followed up.

In summary, there is a paucity of reports on LP with lesion distribution along the Blaschko’s lines. The condition is liable to be misdiagnosed as other skin lesions with linear distribution. Few previous reports have described pre- and post-treatment clinical images and dermoscopic photographs. In this report, we present the detailed pre- and post-treatment images, which may facilitate the recognition of this condition.
CONCLUSION
LP with unilateral distribution of lesions along the Blaschko’s lines is a rare entity that needs to be differentiated from other cutaneous lesions with linear distribution. Isomorphism can occur in patients with LP, which may be an important cause for rapid spread of lesions and involvement of multiple segments. Therefore, early diagnosis and treatment are important. Our patient showed considerable improvement in skin lesions with intramuscular glucocorticoid, oral acitretin, topical glucocorticoid, and tretinoin for 4 wk, with no significant side effects. However, no improvement was observed in nail lesion. Long-term follow up is required to assess the treatment efficacy.

ACKNOWLEDGEMENTS
We thank the patient and their family members for their support.

FOOTNOTES
Author contributions: Dong S collected the data, performed the literature search and contributed to the manuscript drafting; Zhu WJ, Xu M, Zhao XQ did the follow up and contributed to the manuscript drafting; Mou Y was involved in treatment of the patient, and revised and reviewed the manuscript; all authors issued final approval for the version to be submitted.

Supported by National Natural Science Foundation of China, No. 81803160.

Informed consent statement: Informed consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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REFERENCES
7 Conforti C, Vezzoni R, Moret A, Retrosi C, Corneli P, Magaton-Rizzi G, Zalaudek I, di Meo N. Dermatoscopic features of
Dong S et al. Unilateral lichen planus along Blaschko’s line


Clinical features and progress of ischemic gastritis with high fatalities: Seven case reports


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Abstract

BACKGROUND
Ischemic gastritis is a clinically rare and highly fatal disease that occurs when the hemodynamics of a patient with vascular risk is disrupted. Early diagnosis and treatment are possible only with upper endoscopy after symptom appearance. We report seven cases of ischemic gastritis and its clinical features, prognosis, and indicators that may help in early detection.

CASE SUMMARY
Of the seven patients, six had vascular risk and five died within 2 wk of diagnosis. Their symptoms included hematemesis and hypotension. Although surgery is a choice for radical treatment, not all patients were tolerant. For such patients, conservative treatment was selected, but all of them died. In contrast, patients who underwent repeat endoscopy showed improved mucosal findings, suggesting that this improvement may not affect prognosis. Some ischemic changes such as wall thickening, mural emphysema, and fluid retention in the stomach were observed before diagnosis through endoscopy and computed tomography (CT). The CT scan can be effective for early detection, and improvement in circulatory
failure and aggressive treatment may save the lives of patients with this disease.

CONCLUSION
The characteristic CT findings enable early detection of ischemic gastritis. Early diagnosis increases the chance of survival if early therapeutic intervention and improvement of circulatory dynamics can be achieved in this highly fatal disease.

Key Words: Celiac artery; Gastrointestinal bleeding; Ischemic gastritis; Superior mesenteric artery; Vascular risk; Case report

Core Tip: Ischemic gastritis is extremely fatal, especially in those with vascular risk. Early diagnosis and treatment is important. However, it is difficult to diagnose early unless the patient is symptomatic. Here we report seven cases of ischemic gastritis, of whom five patients died within 2 wk of diagnosis. Surgery could not be selected for our patients because of their poor general condition; instead, they were treated conservatively. Patients with improved mucosal findings on repeat endoscopy did not show increased survival. Characteristic computed tomography findings enable early detection of this disease.

INTRODUCTION
Ischemic gastritis is a rare event that occurs in the stomach where blood flow is abundant. It has a low early detection and a high mortality rate[1-9]. The risk of ischemic gastritis increases in older adults and patients with vascular risks, such as renal failure and diabetes mellitus[1]. These risks in combination with the hemodynamic disruption contribute to the high mortality rate[8]. The characteristic symptoms of this disease include abdominal pain and gastrointestinal bleeding[10]. Computed tomography (CT) reveals wall thickening, mural emphysema, and fluid retention, but rarely vascular obstruction[2,11]. Upper gastrointestinal endoscopy reveals multiple ulcers and several ischemic changes[4,6]. Surgical treatment with curative intent is sometimes necessary but is often difficult because of the patient’s poor general condition[2,3,7]. Early diagnosis and treatment of ischemic gastritis are difficult because the condition can only be diagnosed by upper gastrointestinal endoscopy when symptoms appear; therefore, early detection with other modalities is desirable. We encountered seven patients (5 men, 2 women; mean age, 75 years; age range, 53-90 years) who were diagnosed with ischemic gastritis between April 2016 and September 2021, at the Shonan Kamakura General Hospital. of this clinically rare disease and herein report its clinical features, prognosis, and indicators for early detection. The present study examined the baseline clinical and laboratory data, medical history, endoscopic and CT findings, treatment, and outcomes. Ischemic gastritis was defined as the endoscopic finding of ischemic changes, such as multiple ulcers, mucosal edema, hemorrhagic mucosa, and fractured congested mucosa[1,2,5]. The vascular risk was defined as the presence of any of the following: diabetes, dyslipidemia, hypertension, chronic kidney disease, hyperuricemia, heart failure, and any vascular disease[1-3,12].

CASE PRESENTATION
Chief complaints
The characteristics of patients with ischemic gastritis are shown in Tables 1 and 2. There were five men and two women, with a mean age of 75 years (range 53-90 years). All patients were older adults, except for one young woman (case 3), who attempted suicide by hanging. Six patients experienced shock at presentation. Only one patient’s systolic blood pressure had dropped below 60 mmHg. The demographic profiles are shown in Table 1.
Table 1 Demographic and clinical data of seven patients

April 2016 to September 2021: n = 7 patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean age of 75 yr (range 53-90 yr)</td>
</tr>
<tr>
<td>Sex</td>
<td>Five men, two women</td>
</tr>
<tr>
<td>Chief complaint</td>
<td>Hematemesis: 7/7 (100%)</td>
</tr>
<tr>
<td>Shock at presentation</td>
<td>6/7 (86%)</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2/7 (28%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2/7 (28%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2/7 (28%)</td>
</tr>
<tr>
<td>Any vascular diseases</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>History of smoking: 2/7 (28%); never smoking: 4/7 (57%)</td>
</tr>
<tr>
<td>Medicine</td>
<td></td>
</tr>
<tr>
<td>Anticoagulants (warfarin)</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>Antiplatelet (aspirin)</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>Endoscopic findings</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>Stomach: 3/7 (43%); esophagus to duodenum: 4/7 (57%)</td>
</tr>
<tr>
<td>Second endoscopy</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>Patients undergoing CT scan before endoscopy</td>
<td>7/7 (100%) On the day: 3; 2 d before: 1; 3 d before: 1; 9 d before: 1; 14 d before: 1</td>
</tr>
<tr>
<td>CT findings</td>
<td>Wall thickening in the stomach: 4/7 (57%); mural emphysema in the stomach: 3/7 (43%)</td>
</tr>
<tr>
<td>Operation before illness onset</td>
<td>4/7 (57%): Splenectomy: 1; Aortic valve replacement: 1; Ascending aorta replacement: 1; Lung cancer operation and superior vena cava repair: 1</td>
</tr>
<tr>
<td>Treatment</td>
<td>Conservative treatment: 7/7 (100%)</td>
</tr>
<tr>
<td>Mechanical assistance</td>
<td>CHDF: 3/7 (43%)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Death: 7/7 (100%)</td>
</tr>
<tr>
<td>Time from onset to death</td>
<td></td>
</tr>
<tr>
<td>1-14 d</td>
<td>5/7 (71%)</td>
</tr>
<tr>
<td>15-28 d</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>-29 d</td>
<td>1/7 (14%)</td>
</tr>
</tbody>
</table>

CT: Computed tomography; CHDF: Continuous hemodiafiltration.

History of present illness

Prior to diagnosis, 7 patients were admitted to our institution for medical care for other conditions. Three patients received ventilatory support. One patient had been on warfarin, one on aspirin. The onset of hematemesis prompted urgent workup with endoscopy, leading to the diagnosis of ischemic gastritis. Four of the seven patients (57.1%) had undergone surgery within one week before onset of illness. The surgeries included splenectomy, aortic valve replacement, ascending aorta replacement, and lung cancer surgery with superior vena cava repair. In addition, two of the four patients underwent surgery on the trophic vessels of the stomach (celiac artery and superior mesenteric artery).
## Table 2 Clinical characteristics of each ischemic gastritis patient

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Shock at presentation</th>
<th>Underlying disease</th>
<th>Operation before onset</th>
<th>Anticoagulants</th>
<th>Antiplatelet</th>
<th>Treatment</th>
<th>Mechanical assistance</th>
<th>Surgery contraindications</th>
<th>Outcome</th>
<th>Time from onset to death (d)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>F</td>
<td>Hematemesis</td>
<td>Yes</td>
<td>CHF, CKD, OCI, diabetes</td>
<td>None</td>
<td>Warfarin</td>
<td>No</td>
<td>Conservative</td>
<td>No</td>
<td>Poor general condition</td>
<td>Death</td>
<td>28</td>
<td>CHF</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>M</td>
<td>Hematemesis</td>
<td>Yes</td>
<td>AAA, OMI</td>
<td>Splenectomy</td>
<td>No</td>
<td>No</td>
<td>Conservative</td>
<td>No</td>
<td>Poor general condition</td>
<td>Death</td>
<td>2</td>
<td>Splenic hemorrhage</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>F</td>
<td>Hematemis</td>
<td>No</td>
<td>Depression</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Conservative</td>
<td>No</td>
<td>Poor general condition</td>
<td>Death</td>
<td>14</td>
<td>Hypoxic encephalopathy</td>
</tr>
<tr>
<td>4</td>
<td>84</td>
<td>M</td>
<td>Hematemesis</td>
<td>Yes</td>
<td>AVS, CKD, CHF, thoracic aneurysm, hypertension</td>
<td>AVR</td>
<td>No</td>
<td>Aspirin</td>
<td>Conservative</td>
<td>CHDF</td>
<td>Poor general condition</td>
<td>Death</td>
<td>12</td>
<td>Multi organ failure</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>M</td>
<td>Hematemesis</td>
<td>Yes</td>
<td>AAA, hypertension</td>
<td>AAR</td>
<td>No</td>
<td>No</td>
<td>Conservative</td>
<td>CHDF</td>
<td>Poor general condition</td>
<td>Death</td>
<td>2</td>
<td>Aspiration pneumoniae</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>M</td>
<td>Hematemesis</td>
<td>Yes</td>
<td>IVF, CKD, hypertension, dyslipidemia, diabetes</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Conservative</td>
<td>No</td>
<td>Poor general condition</td>
<td>Death</td>
<td>2</td>
<td>Myocardiac infarction</td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>M</td>
<td>Hematemesis</td>
<td>Yes</td>
<td>OMI, dyslipidemia, lung cancer</td>
<td>Lung cancer operation (superior vena cava repair)</td>
<td>No</td>
<td>No</td>
<td>Conservative</td>
<td>CHDF</td>
<td>Poor general condition</td>
<td>Death</td>
<td>298</td>
<td>Septic shock</td>
</tr>
</tbody>
</table>

CHF: Chronic heart failure; CKD: Chronic kidney disease; OCI: Old cerebral infarction; AAA: Abdominal aortic aneurysm; OMI: Old myocardial infarction; AVS: Aortic valve stenosis; IVF: Idiopathic ventricular fibrillation; AVR: Aortic valve replacement; AAR: Ascending aorta replacement.

### History of past illness

The clinical characteristics are shown in Table 2. All of the patients had at least one cardiovascular comorbidity (ranging from hypertension to congestive heart failure). Three patients had (medically controlled) arterial aneurysms, two patients had a history of myocardial infarction. Three patients had diabetes mellitus, and two had dyslipidemia. One patient had a history of cerebrovascular disease, and one had vascular surgery related to malignancy. One patient had a history of depression and suicidal attempt resulting in ischemic encephalopathy.

### Personal and family history

The family history was unremarkable.

### Physical examination

All patients had hematemesis and hypotension before the onset of ischemic gastritis.
Laboratory examinations
The blood tests showed no specific issue other than progressive anemia due to hematemesis and an enlarged blood urea nitrogen/creatinine ratio.

Imaging examinations
All patients had at least a CT scan for a different investigation prior to endoscopy. The findings are presented in Table 1.

The characteristics of endoscopic and CT findings are presented in Table 3. All seven patients underwent CT scans before endoscopy, which showed wall thickening, intramural gas appearance, and peri-gastric fluid collection (Figure 1). These findings can indicate ischemic changes in the stomach layers. In four cases, these findings were observed several days before the onset of symptoms such as hematemesis. Upper gastrointestinal endoscopy revealed ischemic changes (Figure 2), which were observed only in the stomach in three patients and between the esophagus and the duodenum in the remaining four patients. In addition, vascular calcification was observed in three of the seven cases; calcification was observed at the origin of the celiac artery, and one case had compression of the celiac artery by the median arcuate ligament. Invasive treatment was difficult due to the patients' general condition, and conservative treatment with gastric mucosal protective agents or proton pump inhibitor administration and fasting fluids was chosen in all cases.

Further diagnostic work-up
A notable improvement in the gastric mucosa was observed only in one patient (case 1), who underwent repeat endoscopy (Figure 3). However, CT findings did not improve despite endoscopic mucosal improvement (Figure 4). Continuous hemodiafiltration was used in three cases to maintain circulatory dynamics; however, two patients died within 2 wk. Five of the seven patients (71.4%) died within 2 wk of onset of ischemic gastritis, and the others eventually died from their respective primary disease. The diagnosis is usually based on pathological findings; however, it is difficult to examine the histology in the presence of hematemesis and hypotension. In the single case when the patient's general condition improved and the endoscopy was repeated, the mucosal findings were improved, and the histological examination did not reveal any signs suggestive of ischemia. Postmortem autopsy could not be performed without family consent. Therefore, the diagnosis of ischemic gastritis was made based on physical examination and imaging tests.

FINAL DIAGNOSIS
The patients were diagnosed with ischemic gastritis after endoscopy.

TREATMENT
The general condition of the patients was poor and surgical treatment was not feasible, so conservative treatment was chosen in all cases.

OUTCOME AND FOLLOW-UP
All seven patients died. However, the immediate cause of death was different in each case. The median time from the onset of symptoms of ischemic gastritis to death was 12 d (range 2-298 d).

Case 1 underwent repeat endoscopy and a notable improvement in the gastric mucosa was observed (Figure 3). However, CT findings did not improve despite endoscopic mucosal improvement (Figure 4). The patient's abdominal symptoms gradually improved, and she was able to eat; nevertheless her circulatory dynamics were not stable, and she eventually died. Case 7, a long-term survivor, suffered vascular injury during lung cancer surgery. Postoperatively, the patient developed renal failure, and although continuous hemodiafiltration (CHDF) was introduced, his general condition did not improve, and he suffered brain death. Although he survived for a relatively long period of time, he eventually died of septic shock. All three cases, in which CHDF was introduced, underwent surgical vascular operations, and were treated for postoperative renal failure.

DISCUSSION
We reported seven cases of ischemic gastritis with a poor prognosis, five of whom died within 2 wk. Since the stomach has an abundant blood flow, it is not prone to ischemia, and not many cases of
Table 3 Endoscopic/computed tomography findings and treatment in each ischemic gastritis patient

<table>
<thead>
<tr>
<th>Case</th>
<th>Longitudinal ulcers</th>
<th>Irregular multiple ulcers</th>
<th>Mucosal edema with redness and erosion</th>
<th>Hemorrhage</th>
<th>Endoscopic distribution</th>
<th>Date of CT scan from endoscopy</th>
<th>CT findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Esophagus to duodenum</td>
<td>On the day</td>
<td>Dilatation and edematous thickening of the wall of duodenum and ileum. Calcification at the origin of the celiac artery</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Stomach</td>
<td>On the day</td>
<td>Hematoma around the spleen</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Stomach</td>
<td>On the day</td>
<td>Fluid accumulation from the stomach to the large intestine. Compression of the celiac artery by the median arcuate ligament</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Esophagus to duodenum</td>
<td>3 d</td>
<td>Wall thickening and mural emphysema and fluid retention in the stomach</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Esophagus to duodenum</td>
<td>9 d</td>
<td>Wall thickening in the stomach</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Esophagus to duodenum</td>
<td>2 d</td>
<td>Wall thickening and mural emphysema and fluid retention in the stomach. Calcification at the origin of the celiac artery</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Stomach</td>
<td>14 d</td>
<td>Wall thickening and mural emphysema and fluid retention in the stomach</td>
</tr>
</tbody>
</table>

CT: Computed tomography.

Figure 1 Abdominal plane computed tomography scans obtained 14 d before the onset of ischemic gastritis in case 1. Computed tomography revealed wall thickening, mural emphysema, and fluid retention in the stomach. The arrow shows the wall thickening. The arrowhead indicates the mural emphysema.

Ischemic gastritis have been reported[1-9]. The gastric blood flow is provided mainly from the celiac trunk, superior mesenteric artery, and some collateral arteries. Furthermore, the stomach has an abundant submucosal vascular plexus, which is more resistant to ischemia than that of the small and large intestines[1].

The causes of ischemic gastritis can be divided into two groups: vascular and intestinal factors. Vascular factors include major arterial and venous occlusions, small vessel lesions, systemic hypoperfusion, shock, and sepsis[1,12]. Iatrogenic cessation of blood supply involves chemoembolization or surgical ligation[2,3], and polyarteritis nodosa, leukocytoclastic vasculitis, and portal hypertension have also been reported[4]. Most of our cases did not involve direct invasion by feeding vessels. The surgical
Figure 2 Upper gastrointestinal endoscopy images performed on hospital day 2 of case 1. A: It showed longitudinal ulcers, multiple irregular ulcers, mucosal edema with redness, erosion, and hemorrhage in the stomach; B: In the duodenum, it showed longitudinal ulcers, multiple irregular ulcers, mucosal edema with redness, erosion, and hemorrhage.

Figure 3 Upper gastrointestinal endoscopy images on hospital day 16 of case 1. A: It revealed improved mucosal findings in the stomach; B: It revealed improved mucosal findings in the duodenum.

Figure 4 Abdominal plane computed tomography scans obtained after improvement of endoscopic findings. It revealed persistent wall thickening and mural edema and significant bilateral pleural effusion.

vascular invasion itself may affect hemodynamics, even if the gastric feeding vessels are not directly manipulated. On the other hand, intestinal factors include increased intragastric pressure[^3]. Decreased gastric motility due to aging or diabetes can cause gastric distention and increased intragastric pressure, which can lead to disease development[^13,14].

[^1]: Shionoya K et al. Ischemic gastritis.
[^2]: WJCC
[^3]: DOI: 10.12998/wjcc.v10.i24.8686 Copyright ©The Author(s) 2022.
In addition to recovery with conservative treatment, some cases also recover with invasive treatment including total gastrectomy\cite{1,5,7,12} or vascular reconstruction by endovascular therapy\cite{9}. Since most patients are in poor general condition, surgical indications need to be carefully examined. In some cases, early death occurs despite improvement in gastric mucosal findings, as in case 3\cite{1,15,16}. Ischemic gastritis is considered as one of the phenotypes associated with impaired systemic blood flow; impaired systemic blood flow occurs in patients with systemic conditions or comorbidities that lead to ischemia of the stomach. Improvements in endoscopic findings may not be directly related to the prognosis. In contrast, CT contributed to the diagnosis of our cases. Wall thickening, mural emphysema, and fluid retention were observed in the stomach, indicating ischemic changes; these were observed on CT scan a few days before symptoms such as hematemesis appeared and persisted even after mucosal recovery on endoscopy, which was considered useful for early diagnosis and subsequent follow-up. As ischemic gastritis is associated with severe systemic arteriosclerosis, improvement of the gastric mucosal surface may not lead to an improved prognosis. In some cases, surgery or endovascular therapy saves the patient’s life, and a CT scan may be able to improve prognosis with early diagnosis and intervention\cite{1,7,9}.

**CONCLUSION**

Herein, we report seven cases of ischemic gastritis, which was diagnosed with upper gastrointestinal endoscopy. However, we revealed that improvement in endoscopic findings may not affect prognosis. Although characteristic CT findings enable early detection of this disease, at the stage when symptoms such as hematemesis appear, the patient’s general condition is often poor, making aggressive therapeutic intervention difficult. Early diagnosis increases the chance of survival if early therapeutic intervention and improvement of circulatory dynamics can be achieved in this highly fatal disease.

**ACKNOWLEDGEMENTS**

The authors wish to thank Ms. Fujii M for her excellent technical and secretarial assistance.

**FOOTNOTES**

**Author contributions:** Shionoya K and Sasaki A contributed to the concept/design; Shionoya K, Sasaki A, Kimura K, Nishino T, Sumida C, Ichita C, and Tsukiyama T contributed to the observation, acquisition of data, and data analysis/interpretation; Sasaki A, Moriya M, Kimura K, Nishino T, Kubota J, Sumida C, Tasaki J, Ichita C, Makazu M, Masuda S, Koizumi K, Kawachi J, and Kako K contributed to the critical revision of the manuscript and approval of the article; Sasaki A supervised the paper; all authors read and approved the final manuscript.

**Informed consent statement:** Informed consent was waived by the Institutional Review Board of the hospitals.

**Conflict-of-interest statement:** The authors declare no conflict or competing interests.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP
REFERENCES


Retinoblastoma in an older child with secondary glaucoma as the first clinical presenting symptom: A case report

Ying Zhang, Li Tang

**BACKGROUND**
Retinoblastoma (Rb) is primarily found in infants or young children. The most common primary presenting sign of Rb is leukocoria. Rb is very rare in children who are 10 years old or older. Timely and correct diagnosis as well as proper treatment are the key factors affecting the prognosis of Rb.

**CASE SUMMARY**
A 10-year-old girl with symptoms of vision loss, redness, swelling and pain in the right eye for 2 mo was admitted to our Department of Ophthalmology. The visual acuity of the right eye was graded as hand movement. The intraocular pressure of the eye was 46.9 mmHg. No substantial space-occupying lesion or characteristic calcified plaque was found in the eye. The patient underwent anterior chamber irrigation under general anesthesia on the same day of admission, and 2 mL of irrigation solution was saved for pathological examination. Histopathological examination of the anterior chamber fluid revealed cancer cells. A diagnosis of Rb with masquerade syndrome was made. The patient underwent enucleation followed by 6 rounds of systematic chemotherapy. A follow-up examination almost 9 years later found no relapse of Rb.

**CONCLUSION**
For older pediatric patients who have secondary glaucoma and uveitis symptoms without a clear cause of the disease and have no space-occupying lesion found by imaging examination, aqueous humor or vitreous humor examination is recommended for timely and correct diagnosis and appropriate treatment.

**Key Words:** Retinoblastoma; Secondary glaucoma; Uveitis; Masquerade syndrome; Older children; Case report

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Core Tip: Retinoblastoma (Rb) is most commonly found in young pediatric patients, and is very rare in patients who are 10 years old or older. Here, we report a case of Rb in a 10-year-old girl with secondary glaucoma and other uveitis symptoms as clinical presenting signs. No obvious space-occupying lesions were found in the eye by imaging examination. However, anterior chamber fluid examination found cancer cells and was decisive in the diagnosis of Rb. This suggests the necessity of aqueous humor or vitreous humor examination in the diagnosis of Rb with atypical clinical symptoms.

INTRODUCTION

Retinoblastoma (Rb) is a type of cancer mostly found in infants or young children and can present unilaterally or bilaterally. It is the most common pediatric eye cancer and primarily originates in the eye, with an incidence of 1:16000 to 1:18000 in newborns[1,2]. It has been reported that two-thirds of Rb is found in patients younger than 3 years old. The incidence of Rb in children 5 years old or older is less than 5%, and it is very rare in children 10 years old or older[3].

Currently, the survival rate of Rb patients in developed countries has reached 95%, while it is only 50% worldwide. In addition to the difference in medical conditions and economic conditions in different countries, misdiagnosis and cancer metastasis were the main reasons for the death of patients. Therefore, timely and correct diagnosis is critical for the prognosis of patients.

The most common clinical symptom of Rb to present first is leukocoria. It represents 90% of the first clinical symptoms of Rb, followed by strabismus, redness and pain, proptosis and other signs[4]. However, in addition to the typical symptoms, Rb can also present with other atypical symptoms, such as conjunctival edema, pseudohypopyon in the anterior chamber, pseudocellulitis of the orbit and secondary intraocular hypertension, which may result in the wrong diagnosis and an inappropriate treatment plan. Current treatment of Rb includes cryotherapy, laser photocoagulation, systemic chemotherapy, enucleation, and local chemotherapy through intraocular, peribulbar and ophthalmic artery interventional approaches. In the present study, we reported a case of Rb in a 10-year-old girl with secondary glaucoma and uveitis symptoms as the presenting clinical signs. The diagnosis and treatment procedures were described and discussed.

CASE PRESENTATION

Chief complaints
A 10-year-old girl was admitted to the Department of Ophthalmology at West China Hospital, Sichuan University, on December 10, 2012, due to vision loss accompanied by redness, swelling, and pain in the right eye.

History of present illness
The patient started to suffer gradual vision loss with redness, swelling, and pain in the right eye 2 mo prior to hospital admission and was diagnosed with uveitis and secondary glaucoma in a local hospital. The prescribed treatment was dexamethasone ophthalmic, Azopt ophthalmic and atropine eye ointment. The symptoms were not relieved after treatment. The patient denied fever, headache, coughing, ulcer, skin diseases or arthropathy during the doctor visit.

History of past illness
There was no remarkable illness history.

Personal and family history
There was no remarkable personal or family history.

Physical examination
At the time of hospitalization, the visual acuity of the patient’s right eye was hand movement; the visual acuity of the left eye was 20/20. Intraocular pressure of the right eye was 46.9 mmHg, and the left eye was 19.8 mmHg (1 mmHg = 0.133 kPa). The result of the ophthalmological examination was as follows: mutton-fat KP grading: ++; anterior chamber cell grading: ++++. Multiple white, round nodules were
Figure 1 Image of the anterior chamber in the right eye on Day 1 after hospitalization. The arrow shows corneal edema with haze. The depth of the anterior chamber was normal. Mutton-fat KP: ++ (arrow); anterior chamber cells: +++ (asterisk).

Figure 2 Color image of the fundus of the right eye. The vitreous body was opaque, the C/D ratio of the optic disk was 0.55, retinal edema with bluish color, and the superior temporal retina was pale with occluded, line-like vessels.

found on the right eye near the pupillary margin on the surface of the iris (Figure 1). The dilated pupil size of the right eye was 5 mm with a slower response to light. The lens was clear, and the vitreous body was opaque. The optic cup/optic disc (C/D) ratio was approximately 0.55. Retinal edema with a bluish color was found in the right eye. The superior temporal retina was pale, with a portion of the vessels being occluded and line-like (Figure 2). No abnormalities were found in the anterior segment or the fundus of the left eye.

**Laboratory examinations**
The white blood cell count was 13.02 × 10^9/L, and the percentage of segmented neutrophils was 65.8%.

**Imaging examinations**
The results of the B-mode ultrasound of the eyes suggested vitreous opacity and retinal edema in the right eye. No obvious space-occupying lesion was found intraocularly in the right eye (Figure 3). Ultrasound biomicroscopy examination found multiple ciliary body cysts (Figure 4). The results of computerized tomography (CT) scanning in the axial view and coronal view suggested normal findings in terms of eyeball shape. No space-occupying, intraocular or intraorbital lesions were found (Figure 5).

**Immunocytochemical examinations**
The pathological examination result was as follows: Cancer cells were seen by the liquid-based smear of the aqueous humor of the right eye. Immunocytochemical staining results found CD56 (+), Syna (+), CgA (+, but sporadic), PCK (-), Des (-), LCA (-), and 70% in terms of Ki-67 positivity.
Figure 3 B-ultrasound image of the right eye. The images show the opacity of the vitreous body (arrow) and retinal edema (asterisk).

Figure 4 Image of ultrasound biomicroscopy examination of the right eye. The result suggested multiple ciliary body cysts (arrow).

Figure 5 Computerized tomography image from axial view and coronal view. No intraocular, space-occupying lesions were found.

**FINAL DIAGNOSIS**

The preliminary diagnosis was secondary glaucoma with undetermined causes, conjunctiva hyperemia and corneal edema with haze in the right eye. The patient underwent an anterior chamber irrigation procedure under general anesthesia on the day of hospitalization. The immunocytochemical examination results revealed cancer cells in the anterior chamber fluid. The final diagnosis was stage E Rb in the right eye based on the histopathological examination result of the enucleated eye tissue and other findings.
TREATMENT

The patient first underwent anterior chamber irrigation under general anesthesia on the same day as hospital admission in the Department of Emergency Medicine. Two milliliters of irrigation solution was saved for pathological examination. After cancer cells were found in the anterior chamber fluid, the patient underwent enucleation and prosthetic eye table implantation surgery in the right eye (affected eye) under general anesthesia. The patient was then transferred to the Department of Oncology for 6 rounds of systematic chemotherapy by intravenous infusion with vincristine, etoposide, and carboplatin once a week.

OUTCOME AND FOLLOW-UP

On the first day after the anterior chamber irrigation procedure, the visual acuity of the right eye (affected eye) was graded as hand movement. The intraocular pressure decreased to 13 mmHg. The cornea was clear. Anterior chamber cell grading was ++. No white nodules were found on the surface of the iris (Figure 6), and the vitreous body was opaque. Fundus examination results showed extensive retinal edema with sporadic bleeding in the macula and subretinal area (Figure 7). No abnormalities were found in the anterior segment or the fundus of the left eye. On the fourth day after the procedure, the intraocular pressure increased to 40 mmHg again. After enucleation and prosthetic eye table implantation, the histopathological examination results of the enucleated eye showed a white mass from the center of the pupil, with a size of 0.3 cm × 0.2 cm × 0.1 cm (Figure 8). No tumor cells were found in the lamina cribrosa of the optic nerve. The patient did not regularly visit the hospital for follow-up visits after chemotherapy.

In September 2021, the patient came to our department for a follow-up visit. The examination found the overall health of the right eye was as follows: a prosthetic eye was implanted into the right eye. No symptoms in the left eye were reported. Eye examination results showed that the size and morphology of both eyes were symmetric, and the position of the prosthetic eye and the eye table in the right eye was proper. The vision of the left eye was 20/63 without correction and 20/20 with correction. Examination results of the left eye were as follows: the intraocular pressure of the left eye was 14.8 mmHg; the cornea and lens were clear; the anterior chamber was clear with normal depth; and no abnormalities were found in the fundus.

DISCUSSION

In the present case, we report a case of stage E Rb with atypical symptoms in a 10-year-old girl. More than 3 dozen Rb patients older than 10 years of age have been reported in the literature. Singh et al.[5] reviewed 24 cases up to 2011. Dominguez-Varela et al.[6] also described one case each in 2021. All were sporadic and, similar to our patient, unilateral[5,6]. Although the cure rate of Rb is relatively high, misdiagnosis and cancer metastasis are the main obstacles for further improvement of the prognosis of Rb. At the late stage, Rb tumor cells can invade the optic nerve and orbital tissue and metastasize to the intracranial region, circulatory system or lymph nodes, thereby endangering patients’ lives[7]. The primary treatment strategy for Rb is enucleation of the affected eye(s), which results in a cure rate as high as 95%[8]. If the tumor mass breaks the sclera and spreads out of the eye or breaks the lamina cribrosa and invades the optic nerve, the tumor is considered extracocular Rb, and systematic chemotherapy and regional radiotherapy are required to treat the patient in addition to eye enucleation. At this stage, the 5-year survival rate is 55%-60%[9].

Typically, a diagnosis of Rb could be made based on the following clinical observations: the patient’s age is younger than 3 years old; the presence of typical Rb symptoms, such as leukocoria and strabismus; yellow or white lesions found in the fundus with spreading lesions in the vitreous body or retina; retina detachment; and intraocular space-occupying lesions or calcified plaques found by imaging examinations. However, in the present case, the patient was 10 years old, and the first clinical symptoms were redness and pain in the right eye caused by acute high intraocular pressure, a result of uveitis. Multiple B-mode ultrasounds or CT examinations failed to find substantial space-occupying lesions or characteristic calcified plaques in the eye, which led to misdiagnosis initially. The diagnosis of malignant tumor combined with masquerade syndrome was made 2 mo after the initial doctor visit by histopathological examination of the anterior chamber fluid. Masquerade syndromes are disorders presenting with clinical symptoms similar to those of uveitis, but the disorders are malignant eye cancers. The syndromes are often seen in Rb, choroidal malignant melanoma, intraocular non-Hodgkin’s lymphoma, and cancers metastasized to the eyes[10,11]. Aqueous humor or vitreous humor examination is the primary method used to distinguish masquerade syndrome from uveitis. Vitreous humor examination is superior to aqueous humor examination in regard to cancer cell screening rate. For diffuse anterior Rb, aqueous humor examination is adequate for diagnosis[12,13].
From this case, we were able to determine several pieces of information. First, the primary cause of misdiagnosis in the present case was the diversity and non-specificity of masquerade syndrome. For patients with secondary glaucoma who do not have a clear cause of the disease and a satisfactory result from the treatment for ocular hypertension, the possibility of cancer should be considered. The key step in treating secondary glaucoma without a clear cause of the disease is to correctly identify the cause of the disease. Second, for older pediatric Rb patients, the symptoms and signs are often not typical for Rb, such as conjunctival edema, pseudohypopyon in the anterior chamber, pseudocellulitis of the orbit and secondary intraocular hypertension. Patients with these symptoms are easily misdiagnosed as uveitis or infectious endophthalmitis. However, the pseudohypopyon presented in this case is different from the hypopyon found in patients with infectious endophthalmitis, which is characterized by yellow or white, thick empyema in the anterior chamber. The manifestations of pseudohypopyon are the accumulation of gray or white, different sized, granular or sponge-like tumor cells seeded in the lower part of the anterior chamber or diffusely seeded in the anterior chamber, the surface of the iris or the surface of the lens. Sometimes snowball-like or lumpy opaque nodules can be found in the vitreous cavity due to the seeding of cancer cells in older pediatric Rb patients. Third, for highly suspected intraocular cancer patients with atypical symptoms but without confirmative imaging examination results, anterior chamber fluid or vitreous fluid examination should be performed as soon as possible to make a correct diagnosis[14]. Last, the primary goal of Rb treatment was saving the patient’s life, followed by the saving of the affected eyes and visual functions. For patients with late-stage Rb, enucleation with systematic chemotherapy and regional radiotherapy is recommended to improve the chance of survival of the patient[15,16].
CONCLUSION

We successfully diagnosed and treated a 10-year-old girl with stage E Rb with secondary glaucoma and other atypical symptoms as the first clinical manifestations. For such patients who have secondary glaucoma without a clear cause, the possibility of a malignant tumor should be considered.

FOOTNOTES

Author contributions: Zhang Y followed the patient and drafted the manuscript; Tang L was responsible for the revision and final approval of the manuscript; all authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

REFERENCES

4. Fabian ID, Onadim Z, Karaa E, Duncan C, Chowdhury T, Scheimberg I, Ohnuma SI, Reddy MA, Sagoo MS. The
management of retinoblastoma. Oncogene 2018; 37: 1551-1560 [PMID: 29321667 DOI: 10.1038/s41388-017-0050-x]


12 Zhang MF. The diagnostic investigations should be efficient for patients with uveitis. Zhonghua Yanke Zazhi 2017; 53: 721-723

13 Yang M, Yan JH. Diagnosis and treatment of masquerade syndrome, an analysis of 14 cases. Zhongguo Shiyou Yanke Zazhi 2012; 30: 994-997


15 Wei WR, Zhou N. Attach importance to standardized treatment of retinoblastoma to improve its treatment outcome. Zhonghua Yanubbing Zazhi 2020; 36: 413-418

Recurrent herpes zoster in a rheumatoid arthritis patient treated with tofacitinib: A case report and review of the literature

Qing-Xia Lin, Hui-Juan Meng, Yun-Yan Pang, Yan Qu

BACKGROUND
Tofacitinib is an oral Janus kinase (JAK) inhibitor that is currently approved by the United States Food and Drug Administration for the treatment of rheumatoid arthritis (RA). Varicella zoster virus reactivation leading to herpes zoster (HZ) is an adverse effect of this drug; however, recurrent HZ at the same site is a rare clinical condition.

CASE SUMMARY
A 70-year-old female RA patient had undergone 1-year of tofacitinib treatment (10 mg daily). About 1 mo after initiation of oral tofacitinib, she developed blisters on the left flank and abdomen and was diagnosed with HZ; antiviral therapy with acyclovir was resolutory. However, 5 d prior to presentation at our hospital, erythema and blisters with severe pain recurred at the same site. Small clustered blisters and bullous were visible on the left lumbar abdomen and perineum, with a pain score of 8 (visual analogue scale). Antiviral, nutritional supplement, analgesic and other treatments led to healing but over an atypically long period (approximately 26 d, vs approximately 1 wk). HZ is a common and serious adverse reaction of JAK inhibitors, but it rarely recurs. Our patient’s experience of HZ recurrence at the same site, with a wider affected area, more severe pain and longer healing period, is inconsistent with previous reports.

CONCLUSION
Same-anatomical site HZ recurrence may occur during oral tofacitinib treatment, with more severe clinical manifestations than in the initial occurrence.

Key Words: Tofacitinib; Herpes zoster; Varicella zoster virus; Recurrent infection; Case report
Core Tip: Herpes zoster (HZ) is caused by the reactivation of varicella zoster virus. We report a case of recurrent HZ in a patient with rheumatoid arthritis treated with oral tofacitinib. This patient’s HZ recurred at the same site, with a wider affected area and more significant pain than the first occurrence. After antiviral therapy, the rash slowly resolved. The characteristics of this case are different to those of HZ induced by tofacitinib summarized and analyzed in the literature. We hope that our report will prompt clinicians to standardize the diagnosis and treatment of HZ during tofacitinib therapy.

Citation: Lin QX, Meng HJ, Pang YY, Qu Y. Recurrent herpes zoster in a rheumatoid arthritis patient treated with tofacitinib: A case report and review of the literature. World J Clin Cases 2022; 10(24): 8703-8708
URL: https://www.wjgnet.com/2307-8960/full/v10/i24/8703.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i24.8703

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized pathologically by synovitis involving multiple joints, often accompanied by persistent joint pain, swelling, and stiffness. This disease occurs at all ages and can cause cartilage destruction and bone erosion, leading to destruction of the joint structure and loss of joint function, which seriously affects the patient’s quality of life[1,2]. The purpose of treatment is to improve joint function and the quality of life. Commonly used drugs mainly include non-steroidal anti-inflammatory drugs, glucocorticoids (GCs), and disease-modifying anti-rheumatic drugs[3]; however, the therapeutic effects are limited and there are many associated adverse reactions.

In recent years, Janus kinase (JAK) inhibitors have been approved for the treatment of a variety of immune-mediated inflammatory diseases, including RA and inflammatory bowel disease[4-6]. Tofacitinib was approved in 2012 for the treatment of adult patients with moderate-to-severe active RA and an inadequate response or intolerance to methotrexate[7]. It blocks the signal transduction of various proinflammatory cytokines in RA by inhibiting the activity of JAK1 and JAK3[8]. It also controls the activity of RA by regulating immune and inflammatory responses, thus reducing synovial inflammation and cartilage damage[9]. As the JAK/STAT signaling pathway is important in cells and is widely involved in cell proliferation, differentiation, and immune regulation[10], severe infections including herpes zoster (HZ) are common adverse reactions of JAK inhibitors such as tofacitinib[11].

HZ is a common skin disease that results from the reactivation of varicella zoster virus (VZV). It is common in middle-aged and elderly people and is characterized by erythema and clustered blisters distributed in bands along one peripheral nerve, accompanied by severe pain. Due to differences in nerve invasion by the virus and different immune status of the body, HZ may appear as bleeding, gangrenous or visceral lesions, among other presentations. However, recurrent HZ is rare and often occurs in immunocompromised people, such as those with human immunodeficiency virus (HIV) infection or organ transplantation[12,13]. HZ often occurs during the use of tofacitinib in patients with diseases such as RA, but recurrent HZ has rarely been reported in the literature[14].

Here, we report a case of recurrent HZ in a patient with RA who developed HZ twice at the same site during treatment with tofacitinib. The second occurrence affected a wider area, caused more severe pain, and followed a longer disease course than the first rash; these many clinical characteristics differed from those described in previous clinical studies.

CASE PRESENTATION

Chief complaints
A 70-year-old female patient presented with erythema and blistering on her left waist and abdomen, which were accompanied by pain.

History of present illness
Five days prior to presentation at our clinic, the patient had developed a small swath of red bullous eruption on the left side of her waist and abdomen, with mild pain (pain score of 3 on the visual analogue scale [VAS 3]). Three days previously, the blisters had rapidly increased, involving the lower back, waist and abdomen, and perineum, accompanied by severe pain (VAS 5). The patient was diagnosed with HZ in the outpatient department and treated with oral acyclovir; however, the area of the lesion continued to expand, blood blisters and bullae appeared, and the pain continued to worsen (VAS 8), which seriously affected the patient’s sleep and daily life.
History of past illness
The patient was diagnosed with RA 3 years ago, and had been treated with prednisone, leflunomide, hydroxychloroquine, adalimumab, and other drugs. One year ago, for economic reasons, adalimumab was discontinued and changed to oral tofacitinib (10 mg daily). Approximately 1 mo after initiation of oral tofacitinib, painful blisters appeared on the left flank and abdomen, which were diagnosed as HZ; the blisters healed 2 wk after treatment with the antiviral drug acyclovir. Following her recovery from HZ, the patient continues to receive tofacitinib. At present, her RA is stable.

Personal and family history
The patient’s personal and family histories were unremarkable.

Physical examination
On physical examination, the patient’s temperature was 36.4°C, pulse rate was 72 bpm, respiratory rate was 17 breaths/min, and blood pressure was 145/85 mmHg. Both knees and wrists were swollen without significant deformity or tenderness. Large areas of edematous erythema could be seen on the left abdomen, left perineal area, and left side of the back, with clustered blisters, bullae, and blood blisters. The herpes rash was distributed in bands and did not exceed the midline of the body surface (Figure 1A–C).

Laboratory examinations
Routine blood tests showed the following: white blood cell count of $3.67 \times 10^9 /L$ (normal: $3.5-9.5 \times 10^9 /L$); lymphocyte percentage of 45.2% (normal: 20%-50%); monocyte percentage of 18.7% (normal: 3%-10%); neutrophil percentage of 35.1% (normal: 40%-75%); C-reactive protein of 7.98 mg/L (normal: 0-10 mg/L); and serum amyloid A level of 19.36 mg/L (normal: 0-10 mg/L). Routine urine tests were negative for protein, glucose, red blood cells and white blood cells. There were no abnormal findings following tests for liver function, renal function, blood lipid level, blood glucose level, electrolytes, rheumatoid factor, immunoglobulin (Ig) A, IgM and IgG levels, complement 3 and 5, lymphocytes (CD3, CD4, and CD8; immunoassay), antistreptolysin-O, and anti-HIV.

Imaging examinations
Chest and abdominal computed tomography scans were normal.

FINAL DIAGNOSIS
Recurrent HZ due to tofacitinib.

TREATMENT
Tofacitinib was discontinued. Foscarnet sodium 2 g (40 mg/kg) was infused intravenously every 8 h and mecobalamin 1500 mg/d was administered for 7 d. The patient had severe pain, and was successively treated with ibuprofen 150 mg/d, gabapentin 1200 mg/d, and tramadol 100 mg/d. After 7 d of treatment, some blisters healed. Antiviral drugs were discontinued, and nutritional supplement and analgesic therapies were continued.

OUTCOME AND FOLLOW-UP
After 26 d of treatment, the HZ lesions completely healed, but the patient still had some pain (VAS 3). At the 3-mo follow-up, the pain had disappeared, but the patient was readmitted due to recurrent abdominal pain and diarrhea, and the possibility of gastrointestinal tumors was not excluded.

DISCUSSION
We report herein a case of recurrent HZ in an RA patient treated with tofacitinib. HZ is an infectious skin disease caused by VZV reactivation. VZV infection in humans is often latent in nerve cells and is protected from attack by the body’s lymphocytes[15]. When the body’s immunity is decreased, VZV reactivation can occur, leading to HZ. In most cases, HZ occurs only once; however, recurrent HZ is sometimes seen in immunocompromised or immunosuppressed people, such as those undergoing chemotherapy for malignant tumors or with HIV infection[13]. The incidence of recurrent HZ has been
Lin QX et al. Recurrent herpes zoster following tofacitinib treatment

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**Figure 1** Clinical manifestations of herpes zoster in our patient, including multiple areas of erythema, blisters, bullae, and blood blisters. A: On the front of the patient, a lesion was present on the left perineum and lower abdomen; B: On the left side of the patient, a lesion was present on the waist; C: On the back of the patient, a lesion was present on the lower back.

reported to be 6.41%, with a predominance in women[16]. The specific mechanism of HZ recurrence is not clear. Current studies suggest that it may be caused by weakening of the body’s immune response to VZV after the occurrence of HZ, or by a decrease in the body’s specific immunity to VZV with increasing age[17].

The risk of HZ is nearly 2-fold higher in RA patients than in those without RA[18]. The use of immunosuppressive medications, especially GCs, can increase the occurrence of HZ in patients with RA, whereas patients treated with biological therapy may develop severe HZ, with the greatest risk in the initial stage[19]. Tofacitinib can also significantly increase the incidence of HZ in patients[20]. The specific mechanism by which tofacitinib increases the risk of infection is not clear and may be related to its inhibition of the JAK/STAT signaling pathway, resulting in reduced downstream signaling and cytokine immune responses to viral infections[21]. Patients treated with tofacitinib have decreased neutrophils, lymphocytes, and natural killer cells[22,23], which may predispose them to VZV activation. The cellular immunity and humoral immunity tests provided values in the normal range for our patient, suggesting that the cause of VZV reactivation was not the persistent immunosuppression due to her RA but, instead, to a tofacitinib-induced abnormal immune reaction leading to HZ; this hypothesis has also been cited in the literature[24]. Patients treated with 10 mg tofacitinib twice daily have a 2.5-fold higher risk of developing HZ compared with 5 mg twice daily in the first 3 mo, whereas the risk is comparable after 6 mo[25]. The risk of HZ is doubled when tofacitinib is used in combination with GC therapy[26], and the incidence of HZ is higher in Japan and South Korea than in Europe[25,27]. Therefore, it is recommended that tofacitinib be used while avoiding concomitant use of GCs. Female sex, increasing age, prior biological exposure, prednisone > 7.5 mg/d, prior outpatient infection, and a greater number of hospitalizations are associated with an increased risk of HZ, and tofacitinib is associated with a nearly 2-fold higher risk of HZ compared with other biological therapies[26,29]. Although the risk of HZ is increased with tofacitinib, there have been few cases of severe, disseminated, and multiganglionic zoster, which recover quickly after antiviral therapy[30]; however, the occurrence of recurrent HZ has not been reported.

Previous studies have shown that recurrent HZ has a shorter course, more localized skin lesions, less pain, and a lower risk of postherpetic neuralgia than primary HZ[17]. However, our patient had many different characteristics than the other clinical cases in the literature, including more extensive skin lesions, more severe pain, longer course of disease, and recurrence at the same site. We speculate that these characteristics may be related to oral tofacitinib. Genetic analysis of RA or psoriatic arthritis treated with tofacitinib identified multiple genetic loci associated with an increased risk of HZ. Variants near the immune-relevant gene cluster of differentiation 83 in European populations and near interleukin 17 receptor B in East Asian populations may contribute to the increased risk of HZ, demonstrating that genetic factors play a role in causing VZV reactivation during tofacitinib treatment [31]. To address the problem of VZV reactivation during treatment with tofacitinib, it is recommended that patients be given a HZ vaccine when tofacitinib or combination systemic treatment is used[32]. It is recommended that live HZ vaccine be injected in patients with RA 2-3 wk before the use of tofacitinib, which can produce significant cellular and humoral immunity, and its safety and efficacy have been confirmed[33].

Our case is a reminder that HZ vaccine should be administered promptly, and clinicians should always be alert to the possible reactivation of VZV before using tofacitinib in elderly patients with previous immunosuppression. The specific genetic and immune mechanisms of HZ recurrence caused by tofacitinib need to be studied further.
CONCLUSION
Tofacitinib can cause recurrent HZ, which may be associated with an immunosuppressive state due to JAK/STAT signaling. We present a rare case of recurrent HZ at the same site, with a more severe and extensive rash, more significant pain, and a longer course than the primary outbreak. The characteristics of this case are inconsistent with previous literature reports. Clinicians should be aware of this condition in patients receiving tofacitinib treatment.

FOOTNOTES
Author contributions: Lin QX and Meng HJ served as the patient’s dermatologists during hospitalization; Pang YY was responsible for the data collection; Lin QX contributed to manuscript drafting and continuous writing of the paper; Qu Y was responsible for revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

Supported by the Doctoral Startup Fund of Affiliated Hospital of Weifang Medical University, No. 2021BKQ01.

Informed consent statement: Informed consent was obtained from the patient and her family for the publication of this case report and any accompanying images.

Conflict-of-interest statement: The authors declare no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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REFERENCES
Lin QX et al. Recurrent herpes zoster following tofacitinib treatment


28 Colombel JF. Herpes Zoster in Patients Receiving JAK Inhibitors For Ulcerative Colitis: Mechanism, Epidemiology, Management, and Prevention. Inflamm Bowel Dis 2018; 24: 2173-2182 [PMID: 29788127 DOI: 10.1093/ibd/izy150]


Intra-abdominal ectopic bronchogenic cyst with a mucinous neoplasm harboring a GNAS mutation: A case report

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Specialty type: Gastroenterology and hepatology
Provenance and peer review: Unsolicited article; Externally peer reviewed.
Peer-review model: Single blind
Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 2, 2
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0
P-Reviewer: Feng J, China; Navarrete Arellano M, Mexico
Received: March 10, 2022
Peer-review started: March 10, 2022
First decision: April 10, 2022
Revised: April 23, 2022
Accepted: July 18, 2022
Article in press: July 18, 2022
Published online: August 26, 2022

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Abstract

BACKGROUND
Bronchogenic cysts are congenital cysts caused by abnormal sprouting from the ventral foregut during fetal life. They usually occur in the mediastinum or lung, but there are very rare cases of ectopic bronchogenic cysts that develop in the abdominal cavity. A unique intra-abdominal ectopic bronchogenic cyst with a mucinous neoplasm that was producing carcinoembryonic antigen (CEA), harboring a GNAS mutation, is reported. The present case may contribute to clarifying the mechanism of tumorigenesis and malignant transformation of ectopic bronchogenic cysts.

CASE SUMMARY
In 2007, a man in his 50s was incidentally found to have an intra-abdominal cystic mass, 8 cm in diameter. Surgical resection was recommended, but he preferred to remain under observation. In 2020, his serum CEA level increased to 26.7 ng/mL, and abdominal computed tomography showed a 15 cm × 12 cm, multifocal, cystic mass located predominantly on the lesser curvature of the stomach. Since malignancy could not be ruled out, he finally underwent surgical resection. Histologically, the cystic wall was lined by ciliated columnar epithelium, accompanied by bronchial gland-like tissue, bronchial cartilage, and smooth muscle. Part of the cyst consisted of atypical columnar epithelium with an MIB-1 index of 5% and positive for CEA. Moreover, a GNAS mutation (p.R201C) was detected in the atypical epithelium, leading to a diagnosis of an ectopic
Bronchogenic cyst with a low-grade mucinous neoplasm. The patient is currently undergoing outpatient follow-up without recurrence.

**CONCLUSION**

An extremely rare case of an abdominal bronchogenic cyst with a low-grade mucinous neoplasm harboring a GNAS mutation was reported.

**Key Words:** Congenital, hereditary, and neonatal diseases and abnormalities; Ectopic bronchogenic cyst; Abdominal neoplasms; GNAS mutation; Carcinoembryonic antigen; Case report

**Core Tip:** A man in his 60s had an intra-abdominal, 15-cm, multifocal, cystic mass located on the lesser curvature of the stomach, and he underwent surgical resection. Histologically, the resected cystic wall was lined by ciliated columnar epithelium, accompanied by bronchial gland-like tissue, bronchial cartilage, and smooth muscle. Part of the cyst consisted of atypical columnar epithelium with an MIB-1 index of 5% that was positive for carcinoembryonic antigen. Moreover, a GNAS mutation (p.R201C) was detected in the atypical epithelium, leading to a diagnosis of an ectopic bronchogenic cyst with a low-grade mucinous neoplasm.

**INTRODUCTION**

Bronchogenic cysts are congenital cysts caused by abnormal sprouting from the ventral foregut during fetal life from the 3rd to 7th weeks[1]. Bronchogenic cysts usually occur in the mediastinum or lung, but there are rare cases of ectopic bronchogenic cysts that develop in the abdominal cavity or retroperitoneum[2,3]. There are some reports of malignant transformation in bronchogenic cysts, but the mechanism of tumorigenesis and malignant transformation is still unknown[1]. An extremely rare case of an intra-abdominal ectopic bronchogenic cyst with carcinoembryonic antigen (CEA) production, in which a mucinous neoplasm harboring a GNAS gene mutation was observed, is presented. The present case may contribute to clarifying the mechanism of tumorigenesis and malignant transformation of ectopic bronchogenic cysts.

**CASE PRESENTATION**

**Chief complaints**

The patient had no symptoms.

**History of present illness**

A man in his 50s underwent magnetic resonance imaging (MRI) for the follow-up of chronic pancreatitis in 2007 and was incidentally found to have an 8-cm-diameter intra-abdominal mass. His physician referred him to the Department of Surgery, but he preferred to remain under observation because he had no symptoms. In 2020, his serum CEA level increased to 26.7 ng/mL, suggesting possible malignancy, and he was finally referred to our department.

**History of past illness**

The patient had a history of gastroesophageal reflux disease and thoracic compression fracture.

**Personal and family history**

The patient had no relevant family history.
Figure 1 Abdominal magnetic resonance imaging findings in 2007. Axial and coronal views of magnetic resonance imaging T2-weighted images show a multifocal, cystic mass with a diameter of 8 cm between the stomach and left lateral lobe of the liver. The white arrowhead indicates the mass. A: Axial view; B: Coronal view.

Figure 2 Abdominal contrast-enhanced computed tomography and endoscopic findings in 2020. A and B: Coronal view of abdominal contrast-enhanced computed tomography shows that the size of the mass has increased to 15 cm (white arrowhead). Part of the wall of the mass shows thickness and contains calcification, but no obvious intracystic nodules are seen. Stomach and pancreas were compressed (orange arrows); C: Esophagastroduodenoscopy shows that the lesser curvature of the stomach is compressed by the mass (white arrowhead).

Physical examination
A large, soft mass was palpable in the left upper quadrant.

Laboratory examinations
The CEA level was elevated to 26.7 ng/mL, whereas the carbohydrate antigen (CA)19-9 level was within the normal limit. Blood counts, blood biochemistry, and coagulation function were all normal.

Imaging examinations
MRI T2-weighted imaging showed a high-intensity, multifocal, cystic mass between the stomach and lateral lobe of the liver (Figure 1). A mass the size of a child’s head was palpable in the left upper quadrant, but he had no symptoms. Contrast-enhanced computed tomography (CT) showed that the multifocal cystic mass had increased to 15 cm in diameter, and part of the cystic wall showed calcification and partial thickness, but there were no obvious intra-cystic nodules (Figure 2A and B). The surrounding organs such as the stomach, pancreas, and liver were markedly compressed by the mass, but the borders of the mass were clear.

Endoscopic examinations
Esophagastroduodenoscopy showed compression of the lesser curvature, but no neoplastic lesions were found in the gastric mucosa (Figure 2C). Colonoscopy did not show any neoplastic lesions.

FINAL DIAGNOSIS
The final diagnosis was an intra-abdominal ectopic bronchogenic cyst with a low-grade mucinous neoplasm harboring a GNAS mutation.
TREATMENT

These findings suggested that the primary site of the tumor was within the lesser omentum. Although he was not diagnosed definitely, malignancy was suspected due to the increasing size of the mass and elevated CEA level. Therefore, he finally underwent surgical resection after his informed consent was obtained.

After laparotomy and resection of the lesser omentum, a smooth-surfaced mass, 15 cm in diameter, was exposed. Most of the mass was loosely attached to surrounding organs and easily dissected, though the mass adhered to the lesser curvature of the stomach (Figure 3A). Therefore, partial resection of the seromuscular layer of the stomach was required to remove the mass (Figure 3B). The defected seromuscular layer was sutured. The operation time was 2 h and 46 min, and intraoperative bleeding was 450 g.

Pathological examinations

On gross examination of the resected specimen, the mass was multifocal and filled with viscous mucus, with size of 15 cm × 12 cm × 12 cm and weight of 1240 g (Figure 3C). Part of the cystic wall consisted of cartilage (Figure 3D). Histologically, the majority of the cystic wall was lined by ciliated columnar epithelium, and bronchial gland-like tissue, cartilage, and smooth muscle were observed in the deeper layer, leading to the diagnosis of an ectopic bronchogenic cyst (Figure 4A and B). Meanwhile, part of the cystic wall, about 5 cm in size, was lined by high columnar epithelium containing mucus in the cytoplasm (Figure 4C and D). This columnar epithelium was folded, making papillary structures, which was considered to be a low-grade mucinous neoplasm. The MIB-1 index was 5% at the site of the low-grade mucinous neoplasm (Figure 5A). Immunohistochemical staining showed that the area with the low-grade mucinous neoplasm was positive for CK20 and CDX2, and negative for CK7, indicating intestinal metaplasia (Figure 5B and C). In addition, the neoplastic lesion showed positive staining for CEA, suggesting CEA production (Figure 5D).

Gene mutation analysis

GNAS mutation analysis by the Sanger method of the lesion with the low-grade mucinous neoplasm showed a missense mutation at codon 201 (p.R201C, c.601C>T; c.601C>T; Figure 6).
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Figure 4 Histological findings of the resected specimen. A and B: The majority of the cystic wall is lined by ciliated columnar epithelium, and bronchial cartilage is observed in the deeper layer of the mucosa (A, × 100; B × 400); C and D: High columnar epithelium containing mucus in the cytoplasm is observed in part of the cystic epithelium, considered to be a low-grade mucinous neoplasm (C, × 100; D × 200).

OUTCOME AND FOLLOW-UP

The patient had grade II delayed gastric emptying, but he recovered and was discharged on the 25th postoperative day. His serum CEA level normalized. He continues to be under observation without evidence of recurrence at 1-year follow-up.

DISCUSSION

This is the first report of a case of an intra-abdominal ectopic bronchogenic cyst with a mucinous neoplasm that was producing CEA, harboring a GNAS mutation.

Bronchogenic cysts are congenital cysts that are established by persistent secretion from abnormal sprouting lung buds that lack continuity with the tracheobronchial system during fetal life[4,5]. Most bronchogenic cysts develop in the lungs or mediastinum; if abnormal lung buds sprout before 4 wk of fetal life, bronchogenic cysts are located in the mediastinum, and if they sprout after 4 wk of fetal life, bronchogenic cysts are located in the lungs[6,7]. The thoracic cavity and abdominal cavity are connected by the pericardioperitoneal canal, but they become separated by the diaphragm, which develops from the septum transversum, dorsal esophageal mesentery, and pleuroperitoneal fold by 7 wk of fetal life[6,8,9]. Therefore, intra-abdominal bronchogenic cysts are considered to be caused by abnormally sprouted lung buds that wandered into the abdominal cavity prior to diaphragmatic formation through the pericardioperitoneal canal.

Ectopic bronchogenic cysts are very rare and have been reported to occur in the abdominal cavity, retroperitoneum, neck, tongue, and scapula[10]. Subphrenic ectopic bronchogenic cysts develop more often on the left side of the patient, with fewer intra-abdominal cases than retroperitoneal cases[5]. In 2011, Ubukata et al[5] summarized 12 cases of intra-abdominal bronchogenic cysts, 9 of which were located close to the stomach, suggesting that intra-abdominal bronchogenic cysts tend to develop around the stomach. In a report of a rare case, a bronchogenic cyst attached to the gastric wall was invaded by adjacent gastric cancer[11].

Bronchogenic cysts are visualized as spherical masses with clear borders, but CT values of the cystic contents vary from as low as normal cysts to as high as solid tumors[12]. With regard to MRI, Murakami et al[13] and Martin et al[14] stated that high intensity of cystic contents on T1-weighted images is more useful than CT for differential diagnosis, but there are also some cases with low intensity of cystic contents on T1-weighted imaging. Due to the rarity of intra-abdominal bronchogenic cysts and the diversity of imaging findings, preoperative diagnosis is considered to be extremely difficult[12]. Due to
Figure 5 Immunohistochemical staining at the site of the low-grade mucinous neoplasm. A: The MIB-1 index is 5% at the site of the low-grade mucinous neoplasm (× 200); B-D: The area with the low-grade mucinous neoplasm is positive for CK20, CDX2, and carcinoembryonic antigen (× 200).

Figure 6 GNAS expression analysis by the Sanger method. The Sanger method shows a missense alteration on codon 201 (p.R201C) in the lesion with the low-grade mucinous neoplasm.

the risk of tumor cell dissemination, histological or cytological diagnosis by puncture of cysts is not indicated. The definite diagnosis of bronchogenic cysts is based on histological examination of resected specimens, and they are characterized by a bronchial-like histology such as ciliated columnar epithelium, cartilage, bronchial gland, and smooth muscle in the cystic wall[1].

Since ectopic bronchogenic cysts are extremely rare, details of their prognosis are still unclear. Malignant transformation has been reported in a few cases of retroperitoneal bronchogenic cysts[1]. The tumor diameter of malignant cases (11.7 ± 4.7 cm) was reported to be larger than that of benign cases
mutations have been found in intraductal papillary mucinous neoplasms (IPMNs) of the pancreas, colorectal villous adenomas, gastric pyloric gland adenomas, appendiceal mucinous neoplasms, and a bronchial mucous gland adenoma[22-25]. Most GNAS mutations observed in IPMNs are caused by R201H or R201C mutations, missense mutations at codon 201, which result in reducing intrinsic hydrolytic activity of GSα, prolonging activation of cell proliferation signals[23]. The GNAS mutation is considered to play a central role in mucus production in appendiceal mucinous neoplasms[25]. In the present case, a low-grade mucinous neoplasm was thought to be caused by the GNAS mutation at the site of intestinal metaplasia. Since the GNAS mutation has also been observed in some appendiceal mucinous carcinomas, a low-grade mucinous neoplasm in bronchogenic cysts may undergo malignant transform to mucinous carcinoma[26]. Since this is the first report describing a GNAS mutation in a bronchogenic cyst, further investigation of the association between GNAS mutations and tumorigenesis both in ectopic and normotopic bronchogenic cysts through accumulation of additional cases is expected.

CONCLUSION

An extremely rare case of a huge abdominal bronchogenic cyst with a low-grade mucinous neoplasm harboring a GNAS mutation was reported. The present case may contribute to elucidating the pathogenesis and natural history of ectopic bronchogenic cysts.

FOOTNOTES

Author contributions: Murakami T, Shimizu H, Nojima H, and Yamazaki M performed surgery; Murakami T and Shimizu H contributed to manuscript drafting; Yamazaki K contributed to pathological diagnosis and manuscript drafting; Usui A, Kosugi C, and Shuto K contributed to preoperative diagnosis; Sato T, Obi S, and Koda K contributed to medical follow-up; Murakami T, Shimizu H, and Koda K were responsible for the manuscript revision; all authors made final approval for the manuscript to be submitted.

Informed consent statement: The patient in the present report underwent surgical resection after his informed consent was obtained.

Conflict-of-interest statement: The authors have no conflict-of-interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Country/Territory of origin: Japan
REFERENCE


Effects of intravascular photobiomodulation on motor deficits and brain perfusion images in intractable myasthenia gravis: A case report

Chiao-Hsin Lan, Yu-Che Wu, Cheng-Chun Chiang, Shin-Tsu Chang

Abstract

BACKGROUND
Myasthenia gravis (MG) is an autoimmune disorder caused by neuromuscular junction failure characterized by muscle weakness and fatigability. We herein report a case of MG that received intravascular laser irradiation of blood (ILIB) interventions and regained muscle power and better quality of life. To our knowledge, no previous study has investigated the benefits of ILIB treatment on patients with MG. We also evaluated the changes in brain perfusion scan and the MG activities of daily living (MG-ADL) and quantitative MG (QMG) scales.

CASE SUMMARY
A 59-year-old man presented to our outpatient hospital experiencing ptosis, diplopia, fibromyalgia, muscle fatigue, and fluctuating weakness in his limbs for 1 year. Based on his history, physical examination, and laboratory investigations, the final diagnosis was a flare-up of MG with poor endurance and muscle fatigue. The patient agreed to receive ILIB. Brain single-photon emission computed tomography (SPECT) was performed both before and after ILIB therapy. After receiving three courses of ILIB, the brain SPECT images showed greatly increased perfusion of the frontal lobe and anterior cingulate gyri. The patient’s MG-ADL scale score decreased markedly from 17/24 to 3/24. The QMG scale score also decreased remarkably from 32/39 to 9/39. The symptoms of MG became barely...
detectable and the patient was able to perform his activities of daily living and regain muscle power.

**CONCLUSION**

ILIB might have beneficial effects on MG, and brain SPECT images provided direct evidence of a positive correlation between ILIB and clinical performance.

**Key Words:** Myasthenia gravis; Intravascular laser irradiation of blood; Myasthenia gravis activities of daily living scale; Quantitative myasthenia gravis scale; Single-photon emission computed tomography; Case report

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**INTRODUCTION**

Myasthenia gravis (MG) is an autoimmune disease that occurs due to the failure of neuromuscular transmission resulting from antibodies against the acetylcholine receptor, muscle-specific kinase, lipoprotein-related protein 4, or agrin in the postsynaptic membrane at the neuromuscular junction[1-4]. During the initial lifetime course of MG, patients often present with ocular symptoms of ptosis and diplopia[5,6]. About half of these patients progress to generalized disease within 2 years[7]. The clinical manifestation of this disorder is fluctuation and variable weakness in the ocular, bulbar, limb, and respiratory muscles, which lead to major symptoms such as dysarthria, dysphagia, fatigable chewing, fatigable limb, or axial weakness. Skeletal muscle fatigue manifests as weakened muscle contractile force[8-10].

The conventional treatment of MG usually includes a combination of symptomatic therapy with acetylcholinesterase inhibitors (e.g., pyridostigmine), immunosuppressive drugs, and immunotherapy using either intravenous immunoglobulin (IVIG) or plasma exchange in selected patients thymectomy [10-14]. The common therapeutic goal of these treatments is to help patients return to normal function as soon as possible while minimizing the side effects. However, patients receiving these treatments often experience adverse side effects and have difficulties in recovering[15].

A novel alternative therapy is intravascular photobiomodulation, also known as intravascular laser irradiation of blood (ILIB). ILIB treatment utilizes a helium-neon laser with a wavelength of 632.8 nm (red light). An optic fiber is inserted into a superficial vein to deliver the laser light[16]. ILIB is considered an alternative treatment for diseases such as chronic spinal cord injury, cerebral stroke, traumatic brain injury, rheumatoid arthritis, chronic Sjögren’s syndrome, fibromyalgia, and chronic pain conditions, due to its effects in increasing microcirculation and improving oxygen supply[17-21]. Before this case, the usefulness of ILIB in patients with MG had not been reported. This study presents a case diagnosed with MG that was treated with ILIB therapy, which resulted in regained muscle power and improved quality of life.

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**CASE PRESENTATION**

**Chief complaints**

A 59-year-old man experienced ptosis, diplopia, fibromyalgia, muscle fatigue, and fluctuating limb weakness for 1 year. Worsening weakness in bilateral lower limbs caused walking disability. The patient
then came to our outpatient hospital in hopes of regaining muscle power and better walking ability.

**History of present illness**
The patient's symptoms had started 1 year ago with recurrent episodes of weakness in four limbs. His eyelid dropped soon after he woke up and double vision appeared spontaneously. He also required a ventilator to maintain his daily sleeping.

**History of past illness**
The patient was initially diagnosed with MG on August 5, 2018, accompanied by severe ptosis, diplopia, and fibromyalgia. He visited a neurologist in a local medical center, who prescribed acetylcholinesterase inhibitor, pyridostigmine (oral: 60 mg/tab, 2 tabs three times daily), for 1 year. Later, the patient was treated with immunosuppressive drugs; namely, rituximab (intravenously: 375 mg/m², once weekly for 4 wk), and received six courses of IVIG to improve his conditions. However, the severe ptosis, diplopia, and fibromyalgia persisted without any sign of recovery. The patient reported no improvements in the weaknesses of his bilateral lower limbs, which caused walking disability and muscle fatigue, which severely affected his daily life.

**Personal and family history**
The patient had no significant personal or family history.

**Physical examination**
During his visit, the MG activities of daily living scale (MG-ADL scale)[22] total score was 20/24 (Figure 1, Table 1), while that for the quantitative MG scale (QMG scale)[23] was 32/39 (Figure 2, Table 2). The patient’s vital signs were within the normal ranges. Repetitive stimulation test at 3 Hz revealed decremental responses (11.8%) in both orbicularis oculi muscles but not in the right abductor pollicis brevis muscle, which suggested the need to consider post-synaptic neuromuscular junctional disorder.

**Laboratory examinations**
Laboratory evaluation revealed positivity for acetylcholine receptor antibody (5.97 nmol/L). The blood biochemistry examinations revealed mildly decreased complement C3 (74.8 mg/dL) levels compared to normal values (79–152 mg/dL). The urine analysis showed normal values.

**Imaging examinations**
No abnormalities were noted on electrocardiograms and chest X-rays. Regional cerebral perfusion
### Table 1 Myasthenia gravis activities of daily living scale

<table>
<thead>
<tr>
<th>MG-ADL scale</th>
<th>Before ILIB intervention</th>
<th>After ILIB intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talking</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chewing</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Swallowing</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Breathing</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Impairment of ability to brush teeth or comb hair</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Impairment to arise from a chair</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Double vision</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Eyelid droop</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>3</td>
</tr>
</tbody>
</table>

The effect of intravascular laser irradiation of blood was assessed using the myasthenia gravis activities of daily living scale for the following eight criteria: talking, chewing, swallowing, breathing, brushing teeth or combing hair, rising from a chair, double vision, and eyelid droop. The numbers in the table represent grades from the maximum of 3 to the minimum of 0. MG-ADL: Myasthenia gravis activities of daily living; ILIB: Intravascular laser irradiation of blood.

### Table 2 Quantitative myasthenia gravis scale

<table>
<thead>
<tr>
<th>Quantitative MG scale</th>
<th>Before ILIB intervention</th>
<th>After ILIB intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double vision sec.</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Ptosis sec.</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Facial muscles</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Swallowing</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Head, lifted sec.</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Right arm outstretched sec.</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Left arm outstretched sec.</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Onset of dysarthria</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Right leg outstretched</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Left leg outstretched</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vital capacity (male)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Right hand grip</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Left hand grip</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>9</td>
</tr>
</tbody>
</table>

The effect of intravascular laser irradiation of blood was measured based on 13 criteria from the quantitative myasthenia gravis scale. The numbers in the table represent grades from the maximum of 3 to the minimum of 0. MG: Myasthenia gravis; ILIB: Intravascular laser irradiation of blood.

(rCBF) scans by brain single-photon emission computed tomography (SPECT) were performed 30 min after the intravenous injection of 30.8 mCi Tc-99m ECD. Easy Z-score Imaging System was used for statistical analysis. The first brain SPECT showed decreased rCBF in the frontal regions and anterior cingulate gyri (Figures 3 and 4). Magnetic resonance imaging of the chest showed no evidence of a thymic mass.

**Further diagnostic work-up**

The results of the antinuclear autoantibodies (ANA) test were negative. The levels of RA factor (serum) were within normal limits (< 20 IU/mL). The levels in anti-cyclic citrullinated peptide (anti-CCP) screening were also normal (0.6 U/mL). The patient was negative for HLA-B27. Finally, the result of the myositis 16-specific Ag panel was unremarkable.
Figure 2 Quantitative myasthenia gravis scale. The effect of intravascular laser irradiation of blood was measured using 13 criteria of the quantitative myasthenia gravis scale. MG: Myasthenia gravis; ILIB: Intravascular laser irradiation of blood.

Figure 3 Regional perfusion brain single-photon emission computed tomography before and after therapeutic intravascular laser irradiation of blood intervention (sagittal view). The white to red and green to blue areas indicate high and low perfusion, respectively. A: The first single-photon emission computed tomography (SPECT) (before ILIB intervention) shows perfusion deficits in the frontal lobe (white arrows); B: The second SPECT [after the third course of intravascular laser irradiation of blood (ILIB) intervention] shows more blood flow in the frontal lobe (white arrows). ILIB: Intravascular laser irradiation of blood.

FINAL DIAGNOSIS

Based on the patient’s history, physical examinations, and laboratory investigations, the final diagnosis...
of the presented case was a flare-up of MG with poor endurance and muscle fatigue (Figure 5).

TREATMENT

The patient was advised to undergo ILIB and agreed. He received three courses of ILIB (60 min each session for 10 consecutive days per course, with a rest interval of 1–2 wk). A helium-neon (He-Ne) laser illuminator (TAIX He-Ne Laser, YJ-ILIB-5, Bio-ILIB Human Energy Corporation, Taiwan) was applied with a wavelength of 632.8 nm, energy of 12.6 to 14.4 J, energy density of 6428.57 J/cm², power output of 2.5–3.5 W/cm², power intensity of 1.79–2.04 W/cm², and irradiation time of 3600 s/session [20]. The laser power was adjusted depending on the patient’s responses.

OUTCOME AND FOLLOW-UP

After completing three courses of ILIB, the patient’s double vision and eyelid-dropping were remarkably improved, with his MG-ADL scale total score decreasing from 17/24 to 3/24. The weaknesses in both upper and lower limbs changed as anticipated. In the QMG scale, the time for both arms outstretched (90° standing) increased from 0–10 s to 90–240 s, while that for both legs’ outstretched (45° supine) increased from 0–10 s to 90–240 s. The patient’s breathing also improved. The algesia of both arms caused by fibromyalgia was also alleviated. Notably, the second total score of the QMG Scale decreased from 32/39 to 9/39. The second brain SPECT showed increased activities in the frontal regions and anterior cingulate gyri (Figures 3 and 4). The patient is content with the efficacy of ILIB treatment.
**DISCUSSION**

After several years of conventional treatments, including acetylcholinesterase inhibitors and immunosuppressive drugs without subjective improvement, the relatively rapid improvement in motor and respiratory function during ILIB treatment in our case suggests that the patient benefited significantly from ILIB therapy. This patient also made great clinical progress, according to his MG ADL and QMG scale scores. This is the first case report on the novel treatment of MG with ILIB. This is also the first study to describe the benefit of ILIB as a treatment for impaired motor function and analgesia by SPECT imaging of a patient with MG.

We used regional perfusion brain SPECT images to assess brain function before and after the ILIB intervention. We observed two intriguing findings in this study of a patient with MG.
First, we observed remarkably increased perfusion in the motor areas of the frontal lobe (Figure 3), which indicated a strong relationship between motor function and frontal lobe activity. Recent studies showed that ILIB therapy improved regional cerebral blood flow and provided faster repair of the affected nervous system through increased ATP production[24,25]. The motor cortex comprises three different areas of the frontal lobe, immediately anterior to the central sulcus. These areas are the primary motor cortex (Brodmann’s area 4), the premotor cortex (PMC), and the supplementary motor area (SMA)[26]. Our SPECT images showed significantly increased perfusion in both the SMA and PMC after ILIB therapy, suggesting that blood flow might re-perfuse, contributing to the improvement in muscle weakness and fatigue.

Second, the SPECT images also showed higher activity in the anterior cingulate cortex (ACC) after ILIB therapy (Figure 4), which indicated a correlation between pain relief and the ACC. Davis et al.[27] reported that the signal intensity changes within the ACC were correlated with pain intensity, sensory, cognitive processes, and motor function including voluntary movement[28]. Hence, higher activities in the ACC, considered a complicated integrative center, showed a re-distribution of blood flow in the brain, which resulted in pain relief in both arms and regained power in the skeletal muscles.

Furthermore, ILIB is considered a treatment that facilitates circulation in the frontal area of the cortex, especially in this case. ILIB may enhance muscular strength and relieve fluctuating and variable fatigue [29,30]. ILIB also plays a role as an immunomodulator through direct or indirect effects on the immune system[21], which was unbalanced in our case with MG. The post-treatment imaging study revealed that ILIB effectively facilitated circulation around the frontal area of the cortex, which improved the clinical symptoms of this patient with MG.

However, the role of the peripheral mechanism in contributing to the recovery of muscle power cannot be ignored. To sustain muscle contraction, ATP needs to be regenerated at a rate complementary to ATP demand. Three major ways are used to replenish ATP in muscle. These systems—phosphagen, glycolytic, and mitochondrial respiration—differ in the substrates used, products, maximal rate of ATP regeneration, capacity of ATP regeneration, and associated contributions to fatigue[31,32]. In addition, ILIB therapy has been reported to promote total cellular ATP synthesis, and antioxidant activity, which contributes to the alleviation of chronic conditions, such as chronic spinal cord injury and fibromyalgia [17,20]. Therefore, we believe that ILIB therapy might enhance muscle power by increasing ATP synthesis in the peripheral mechanism.

CONCLUSION

MG is an autoimmune disease that previously lacked effective treatments and detailed brain perfusion images. Our case showed the feasible management of this condition with ILIB treatment. The brain perfusion scan demonstrated increased activity in the prior deficit of the brain lesion. ILIB might have beneficial effects on MG and SPECT images could be a good monitor for any deficits in the brain.

FOOTNOTES

Author contributions: Lan CH reviewed the literature and contributed to manuscript drafting; Lan CH, Wu YC, and Chiang CC analyzed and interpreted the imaging findings; Chang ST were responsible for the revision of the manuscript for important intellectual content and supervised the study and managed the project; and All authors issued final approval for the version to be submitted.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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REFERENCES


Spontaneous acute epidural hematoma secondary to skull and dural metastasis of hepatocellular carcinoma: A case report

Guang-Zhao Lv, Guo-Chao Li, Wei-Tai Tang, Dong Zhou, Yong Yang

Abstract

BACKGROUND
The skull and dura are uncommon sites for the metastasis of hepatocellular carcinoma (HCC). Spontaneous acute epidural hematoma (AEDH) is also very rare. We report here a spontaneous AEDH secondary to skull and dural metastasis of HCC. This case is extremely rare.

CASE SUMMARY
A 48-year-old male patient with a history of HCC developed unconsciousness spontaneously. Head computed tomography showed "a huge AEDH in the left parietal and occipital region with osteolytic destruction of the left parietal bone. Emergent operation was performed to evacuate the hematoma and resect the lesion. Pathological study revealed that the lesion was the metastases from HCC. The patient died of lung infection, anemia, and liver failure 3 wk after operation.

CONCLUSION
Spontaneous AEDH caused by hepatocellular carcinoma (HCC) dural and skull metastases is extremely rare, the outcome is poor. So, early diagnosis is important. If the level of AFP does not decrease with the shrinkage of intrahepatic lesions after treatment, it is necessary to be alert to the existence of extrahepatic metastases. Since most of the patients had scalp and bone masses, physicians should pay attention to the patient's head palpation. Once a patient with the history of HCC had sudden neurological dysfunction, the possibility of spontaneous AEDH caused by the skull and dura mater metastases should be considered. Since hemorrhage is common in the skull HCC metastases, for patients with spontaneous AEDH accompanied by skull osteolytic lesions, it is also necessary to be alert to the possibility of HCC. For AEDH secondary to HCC
metastases, early diagnosis and timely treatment are critical to improve the patients’ outcomes.

Key Words: Spontaneous acute epidural hematoma; Hepatocellular carcinoma; Skull and dural metastasis; Case report

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Core Tip: We present a case of hepatocellular carcinoma (HCC) metastasis to the skull and dura mater with spontaneous acute epidural hematoma (AEDH). This is the first report of spontaneous AEDH secondary to skull and dura mater metastasis from HCC in the Chinese population. Pathological examination provided evidence that the dura mater was one of the targets for HCC metastasis and could also lead to AEDH in addition to the reported skull metastases. We summarize the characteristics of the 8 reported cases worldwide, discuss the possible cause of AEDH, and offer advice for clinical practice.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the common malignant tumors in adults, with a high incidence in Southeast Asia where hepatitis B and C are prevalent[1]. Lung and bone metastases are the most common events in the terminal stage of the disease, but metastasis to the skull and the central nervous system is relatively rare[2]. Although traumatic acute epidural hematoma (AEDH) is quite often, the spontaneous AEDH is extremely rare. We are presenting a case of HCC metastasis to the skull and dura mater with spontaneous AEDH.

CASE PRESENTATION

Chief complaints
A 48-year-old male patient was found to be unconscious and accompanied by vomiting 3 h before admission.

History of present illness
The patient was diagnosed as HCC and received transarterial chemoembolization (TACE) 6 mo ago. 3 h before admission, he was found to be unconscious and accompanied by vomiting. He was transferred to our emergency by ambulance.

History of past illness
The patient had a history of hepatitis B, but did not take regular antiviral therapy as prescribed by the doctor. He was diagnosed as HCC (BCLC stage: B) and received TACE 6 mo ago in another hospital, the detailed treatment records were unavailable. The patient did not follow the doctor's suggestion for comprehensive treatment, nor did he have regular follow-up visits to the doctors.

Personal and family history
No special personal and family history.

Physical examination
On arrival, physical examination revealed that the patient was in deep coma, Glasgow Coma score was 5 (E1V1M3). The left pupil dilated and the light reflection disappeared. No obvious traumatic change was observed on the scalp. A fixed elastic mass was found in the parieto-occipital area, without swelling or ulceration.

Laboratory examinations
Laboratory examination revealed that alanine aminotransferase (ALT) was 80U/L, aspartate aminotransferase (AST) was 77U/L, the γ-glutamine transpeptidase (GGT) was 339 U/L, the albumin
level was 42.6 g/L and the total bilirubin was 10.70 μmol/L. The alpha-fetoprotein of this patient was over 1210 ng/mL. The platelet count of this patient was $132 \times 10^9$/L. The results of coagulation test showed: prothrombin time (PT) 15.20 s, activated partial thromboplastin time (APTT) 36.00 s. Immuno-logical test results for hepatitis B were HBsAg 691.19 IU/mL, HBeAg 0.01 IU/mL, HBeAb 0.75 IU/mL and HBcAg 146.13 IU/mL. The hepatitis B virus-deoxyribonucleic acid of this patient was $3.75 \times 10^4$ copies/mL.

**Imaging examinations**

Head computed tomography (CT) showed "a huge AEDH in the left parietal and occipital region with osteolytic destruction of the left parietal bone" (Figure 1).

**FINAL DIAGNOSIS**

Cerebral hernia, Acute epidural hematoma, skull and dural metastasis of HCC (BCLC stage: C), hepatitis B infection, cirrhosis (Child-Pugh grade A).

**TREATMENT**

The patient received emergency craniotomy to evacuate the hematoma. During the operation, the parietal bone was found being invaded by a gray-red elastic mass. After removing the bone flap and evacuating the hematoma, the base of the mass was found to be located on the dura mater, with abundant blood supply. The tumor and the invaded dura mater were resected. The base of the tumor was adjacent to the superior sagittal sinus, but did not invade the sinus. No hematoma or tumor invasion was found during the exploration of the subdural space. After resection of the skull lesion, the bone flap was put back and fixed properly.

**OUTCOME AND FOLLOW-UP**

After the operation, the pupils of the patient retracted to normal and were sensitive to light reflection, but the patient remained in light coma and underwent tracheotomy. A comprehensive postoperative examination revealed that the patient had lung and bone metastases. Later, the patient developed secondary lung infection, anemia, and liver failure, and died 3 wk after the operation.

**DISCUSSION**

Regional lymph nodes, lungs and bones are common sites for HCC metastasis. Osseous metastasis of HCC often occurs in vertebrae, pelvis and ribs, the skull is a rare metastatic site for HCC[2]. Spontaneous AEDH is very rare, and may be caused by infection, dural vascular anomalies, tumors or coagulopathies[3]. Most of the reported cases are spinal spontaneous AEDH. Intracranial spontaneous AEDH caused by metastases are extremely rare. Delgado et al[4] reported that epidural hematoma was the first presentation of HCC in a tiny portion of patients. As far as we know, only 8 cases of spontaneous AEDH caused by metastatic HCC have been reported so far, which are summarized below (Table 1). All of the patients were male and over 40 years old, 7/8 cases were from Asian countries, including South Korea and Japan. The geographical distribution of these cases may be related to the epidemiology of hepatitis virus infection. 7/8 patients came to the doctors due to AEDH related symptoms. Only 5/8 of the patients had known histories of HCC. The parieto-occipital region seems to be the preferred metastatic site (5/8). The metastatic HCC is highly invasive, all of the cases had osteolytic changes. Nearly half of the patients had lesions close to the sinus, where the arachnoid particles or the sinus might be eroded by the tumor and lead to hemorrhage. In addition, the lesions located at the base of the middle cranial fossa or the large wing of the sphenoid bone may be related to the erosion of the middle meningeal artery. Impaired liver function induced coagulopathy also contributed to the bleeding in 2 of the patients. The hematomas were huge in most of the cases, 5 of them had deteriorating consciousness and 4 of them developed brain herniation on diagnosis. The outcome of the patients was poor, only 1 patient survived, 1 patient left vegetative state, and the other 6 patients died of liver failure and related complications shortly after operation.

This is the first report of the spontaneous AEDH secondary to the skull and dura mater metastasis from HCC in the Chinese population. In this case, the spontaneous AEDH was huge and developed brain herniation. The patient died of liver failure shortly after the operation. Pathological study revealed that the tumor had a sinusoid structure and the dura mater was invaded by the metastatic tumor.
Table 1 Summary of patients with spontaneous acute epidural hematoma caused by metastatic hepatocellular carcinoma in the literature

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age</th>
<th>Gender</th>
<th>Country</th>
<th>Metastases location</th>
<th>Close to the sinus or MMA</th>
<th>Osteolytic change</th>
<th>Clinical manifestations</th>
<th>Cerebral hernia</th>
<th>Previous diagnosed HCC</th>
<th>Coagulopathy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al</td>
<td>41</td>
<td>M</td>
<td>South Korea</td>
<td>Left parieto-occipital region</td>
<td>Y</td>
<td>Y</td>
<td>Headache, vomiting, drowsiness</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Died of liver failure, 4 mo later</td>
</tr>
<tr>
<td>McIver et al</td>
<td>50</td>
<td>M</td>
<td>United States</td>
<td>Left parietal region</td>
<td>N</td>
<td>Y</td>
<td>Headache, right-sided weakness</td>
<td>N</td>
<td>N</td>
<td>NA</td>
<td>Survive</td>
</tr>
<tr>
<td>Hayashi et al</td>
<td>70</td>
<td>M</td>
<td>Japan</td>
<td>Right parietal bone</td>
<td>N</td>
<td>Y</td>
<td>Headache, left-sided weakness</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Died of liver failure and pneumonia 2 mo later</td>
</tr>
<tr>
<td>Kanai et al</td>
<td>56</td>
<td>M</td>
<td>Japan</td>
<td>Left parieto-occipital region</td>
<td>Y</td>
<td>Y</td>
<td>Headache, deteriorating consciousness</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Died of liver failure 3 wk later</td>
</tr>
<tr>
<td>Nakagawa et al</td>
<td>52</td>
<td>M</td>
<td>Japan</td>
<td>Occipital area</td>
<td>Y</td>
<td>Y</td>
<td>Headache, deteriorating consciousness</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
<td>Died of liver tumor 4 mo later</td>
</tr>
<tr>
<td>Woo et al</td>
<td>46</td>
<td>M</td>
<td>Korea</td>
<td>The greater wing of the right sphenoid bone</td>
<td>Y</td>
<td>Y</td>
<td>Severe headache, deteriorating consciousness</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Died of multi-organ failure 5 d later</td>
</tr>
<tr>
<td>Kim et al</td>
<td>53</td>
<td>M</td>
<td>Korea</td>
<td>Right middle-Cranial fossa floor</td>
<td>Y</td>
<td>Y</td>
<td>Sudden mental deterioration to semicoma</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>Vegetative state</td>
</tr>
<tr>
<td>Nakao et al</td>
<td>58</td>
<td>M</td>
<td>Japan</td>
<td>Left frontal bone</td>
<td>N</td>
<td>Y</td>
<td>Scalp and bone mass</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Died of liver failure 15 mo later</td>
</tr>
</tbody>
</table>

HCC: Hepatocellular carcinoma; M: Male; MMA: Middle meningeal artery; Y: Yes; N: No; NA: Not available.

(Figure 2), which provided the evidence that the dura mater was also a target for HCC metastasis and could also lead to AEDH besides the reported skull metastases. Blood-rich sinusoid structure of HCC and the erosion of the adjacent sinus might contribute to the AEDH in this case. Postoperative coma delayed comprehensive treatment of the primary HCC. Due to the rapid progression of AEDH, timely and effective surgery can save the neurological function of patients to the greatest extent. According to the guiding role of BCLC staging in the treatment and prognosis of HCC, the post-operative Eastern Cooperative Oncology Group performance status (ECOG-PS) of these patients is important to the assessment of anti-cancer effect and expected survival[12]. If neurosurgical procedure restored the performance status to ECOG-PS 0 to 2, these patients could be defined as BCLC grade C, systemic therapy can be beneficial to these patients with the following anti-cancer options: Atezolizumab combined with bevacizumab, sorafenib, and Renvatinib as first-line therapy. Regorafenib and cabozantinib have been recommended as second-line treatments. With systemic anti-cancer treatment, the overall survival of these patients is expected between 8 to 13 mo. If surgical therapy cannot restore the ECOG-PS to under 2, the prognosis of these patients is pessimistic. Best supportive care can only prolong the survival up to 3 mo. So, the early diagnosis and timely treatment of AEDH secondary to HCC metastasis is extremely important. Therapies such as nucleoside analogues and anti-viral agents are also considered beneficial to these patients. Physicians should pay attention to whether the dynamic change of AFP is parallel to the liver associated manifestation. If the intrahepatic nodules shrink after TACE, but the AFP remain stable or even increase with follow-up, extrhepatic metastasis should be considered. A systemic physical examination and multiple organ imaging examinations such as PET/CT allowed these patients to discover the asymptomatic metastases which require timely intervention. Early diagnosis of the metastases is the key to prevent lethal complications such as AEDH.
Figure 1 The head computed tomography scan of the patient showed a huge acute epidural hematoma in the left parietal and occipital region. An osteolytic destruction of the left parietal bone can be found (indicated by the orange arrows).

CONCLUSION

Spontaneous AEDH caused by HCC dural and skull metastases is extremely rare, the outcome is poor. So, early diagnosis is important. If the level of AFP does not decrease with the shrinkage of intrahepatic lesions after treatment, it is necessary to be alert to the existence of extrahepatic metastases. Since most of the patients had scalp and bone masses, physicians should pay attention to the patient's head palpation. Once a patient with the history of HCC had sudden neurological dysfunction, the possibility of spontaneous AEDH caused by the skull and dura mater metastases should be considered. Since hemorrhage is common in the skull HCC metastases, for patients with spontaneous AEDH accompanied by skull osteolytic lesions, it is also necessary to be alert to the possibility of HCC. For AEDH secondary to HCC metastases, early diagnosis and timely treatment are critical to improve the patients’ outcomes.
Figure 2 Pathological examination of the lesion. A: Low-powered picture of the HE staining revealed that the dura mater was invaded by the metastatic tumor; B: High-powered observation of the HE staining showed a sinusoid structure of the metastatic hepatocellular carcinoma. Immuno-histochemistry staining showed that metastatic hepatocellular carcinoma was strongly positive for C: AFP and D: Ki67.

FOOTNOTES

Author contributions: Lv GZ, Li GC and Yang Y were the patient’s neurosurgeons, reviewed the literature and contributed to manuscript drafting; Lv GZ reviewed the literature and contributed to manuscript drafting; Tang WT analyzed and interpreted the imaging findings; Zhou D was responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

Supported by Natural Science Foundation of China, No. 81901250; Natural Science Foundation of Guangdong Province, No. 2019A1515010104 and No. 2022A1515012540; High-level Hospital Construction Project of Guangdong Provincial People’s Hospital, No. DFJH201924; and Science and Technology Program of Guangzhou, No. 202002030128.

Informed consent statement: The patient’s legal guardian provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: We have confirmed all the items on the CARE checklist.

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S-Editor: Xing YX
L-Editor: A
P-Editor: Xing YX
REFERENCES


Malignant melanotic nerve sheath tumors in the spinal canal of psammomatous and non-psammomatous type: Two case reports

Jeong A Yeom, You Seon Song, In Sook Lee, In Ho Han, Kyung Un Choi

Abstract

BACKGROUND
A malignant melanotic nerve sheath tumor (MMNST), previously known as a melanotic schwannoma, is a rare variant of a peripheral nerve sheath tumor composed of Schwann cells with melanotic differentiation. Only a few reports of spinal MMNST have been reported.

CASE SUMMARY
In the first case, a 58-year-old woman presented with a history of low back pain and paresthesia. Magnetic resonance imaging (MRI) and computed tomography (CT) of the lumbar spine revealed an intradural extramedullary mass lesion with amorphous linear calcification. Complete tumor resection was performed and histological examination revealed a psammomatous melanotic schwannoma. In the second case, a 72-year-old man presented with low back pain and paresthesia. MRI of the thoracolumbar spine revealed an intramedullary mass lesion at the T11 vertebral body level. The mass lesion was hypointense on T2WI and hyperintense on T1WI. Tumor resection was performed and the histologic result was melanotic schwannoma.

CONCLUSION
MMNST should be considered in the differential diagnosis when calcification or melanin is seen in an intradural spinal tumor.
INTRODUCTION

Melanotic schwannoma (MS) is a neoplasm of neuroectodermal origin characterized by melanotic pigmentation in the cytoplasm of Schwann cells[1]. MS is an extremely rare type of nerve sheath tumor, accounting for less than 1% of all primitive nerve sheath tumors[2]. MS was first described by Millar in 1932 as a malignant melanotic tumor of ganglion cells which was subsequently termed melanocytic schwannoma in 1975 by Folpe et al[3]. MS was previously classified as a benign tumor in the 2013 WHO classification, but in the 2020 WHO classification, the term “melanotic schwannoma” was revised to “malignant melanotic nerve sheath tumor (MMNST)” due to its malignant behavior[4]. MMNST is a rare aggressive peripheral nerve sheath tumor composed of Schwann cells with melanotic differentiation[5]. Spinal MMNST occurs in the lumbosacral (47.2%), thoracic (30.5%) and cervical (22.2%) regions[6]. Rarely, the intramedullary type is seen. MMNST can be divided into psammomatous (affecting spinal nerves and paraspinal ganglia) and non-psammomatous (affecting autonomic nerves of the viscera and cranial nerves) types[7]. The peak age of presentation is slightly younger (20–50 years) than that for conventional schwannomas[7]. Here, we present two cases of psammomatous and non-psammomatous MMNST that occurred in the spinal canal, focusing on computed tomography (CT) and magnetic resonance (MR) images.

CASE PRESENTATION

Chief complaints
Case 1: A 58-year-old woman presented with a history of low back pain, paresthesia and cold sensation in both legs for several years.

Case 2: A 72-year-old man presented with a 6-mo history of low back pain and paresthesia in both legs.

History of present illness
Case 1: The symptoms were gradual in onset and progressive in nature leading to difficulty in walking. The patient felt abnormal sensations in both legs.

Case 2: The patient had a 6-mo history of low back pain and paresthesia in both legs and a 3-mo history of gait disturbance.

History of past illness
Case 1: The patient did not have any history of trauma or weight loss. She had no history of previous surgery or medications.

Case 2: There was no history of trauma, fever or weight loss. However, the patient had diabetes mellitus and hypertension.

Personal and family history
Cases 1 and 2: These patients had no family history of malignancy.
**Physical examination**

**Case 1:** The patient had normal vital signs and there was no tenderness over the lumbar spine. There was no motor dysfunction in either leg.

**Case 2:** The motor function of the lower legs was grade 4 and anal tone was also decreased.

**Laboratory examinations**

**Case 1:** Laboratory examinations were unremarkable including complete blood count, coagulation profile, C-reactive protein and serum electrolytes. Preoperative laboratory results were all normal.

**Case 2:** The total leukocyte percentage and leukocyte count were in the normal range and the test for rheumatic factor was negative. The erythrocyte sedimentation rate and C-reactive protein levels were also within the normal range.

**Imaging examinations**

**Case 1:** There were no specific abnormal findings on plain radiographs of the thoracolumbar spine. MR imaging (MRI) of the lumbar spine revealed an intradural extramedullary mass lesion measuring 4.1 cm × 1.6 cm × 1.3 cm at the T11-12 Level with low signal intensity (SI) similar to that of the spinal cord on T1-weighted imaging (T1WI) and heterogeneously high SI on T2-weighted imaging (T2WI) (Figure 1A and B). The margins of the masses were well defined. The mass showed heterogeneous enhancement with no centrally enhancing portion on contrast-enhanced imaging (Figure 1C). There was spinal cord compression and displacement by the mass lesion causing compressive myelopathy of the above spinal cord. Amorphous linear calcification was observed in the peripheral margin of the mass lesion on a CT scan of the thoracolumbar spine (Figure 1D). Considering the location and imaging findings of the lesion, myxopapillary ependymoma and calcified meningioma were considered as differential diagnoses.

**Case 2:** Radiographs of the thoracolumbar spine showed findings indicative of ankylosing spondylitis. MRI of the thoracolumbar spine revealed an intramedullary mass lesion with a round shape and eccentric location measuring approximately 1 cm × 0.6 cm × 0.6 cm at the T11 vertebral body level. The mass lesion was hypointense on T2WI and hyperintense on T1WI (Figure 2A-C). Contrast-enhanced images demonstrated homogenous enhancement (Figure 2D). On DWI, the lesion showed a signal void. In the apparent diffusion coefficient (ADC) map, the lesion did not show diffusion restriction (Figure 2E and F). The ADC value was $1.33 \times 10^{-3}$ mm$^2$/s. Melanoma and angioma were considered as differential diagnoses considering the characteristic signal intensity of the lesion.

**Further diagnostic work-up**

**Case 1:** A laminectomy was performed at the T10-12 Level and complete tumor resection was performed under intra-operative neurophysiological monitoring. The tumor was dissected from the adherent surrounding spinal cord. On gross findings, fragments of brownish-white soft tissue were seen. Histological examination revealed epithelioid and spindle-shaped Schwann cells with brownish pigment and psammomatous bodies (Figure 1E). On immunohistochemistry, positive immunoactivity was shown for S-100 protein (Figure 1F) and vimentin. HMB45, Melan-A and GFAP were negative. The Ki67 proliferation index was 7.7%.

**Case 2:** A partial laminectomy was performed at the T11-T12 Level under intraoperative neurophysiological monitoring. In the operative field, a dark black mass attached to the spinal cord was identified. Complete tumor resection could not be performed due to severe adhesion to the spinal cord and thus only a biopsy was performed. Hematoxylin and eosin (H&E) staining revealed spindle-shaped cells with dense melanin pigmentation covering the nucleus and cytoplasm (Figure 2G). Immunohistochemical staining revealed positive immunoactivity for the S-100 protein (Figure 2H). In addition, it was positive for HMB-45 (antimelanoma antibody). The tumor cells were negative for CK, EMA, C34 and SMA.

**FINAL DIAGNOSIS**

**Case 1:** The final diagnosis was psammomatous melanotic schwannoma.

**Case 2:** These findings are compatible with melanotic schwannoma.

**TREATMENT**

**Case 1:** Since the patient underwent complete tumor resection for the diagnosis, the patient did not
Figure 1 A 58-year-old female with psammomatous melanotic schwannoma. A: Axial T1-weighted image of 11-12th thoracic spine level shows low signal mass lesion (arrows) located in the intradural space; B: Axial T2-weighted image shows the mass lesion (arrows) with heterogeneously high signal intensity and the spinal cord (thick arrow) is displaced and compressed by the mass lesion; C: The mass lesion (arrows) represents heterogeneously strong enhancement containing necrotic portion on sagittal fat-suppressed, contrast-enhanced T1-weighted image; D: Amorphous linear calcification (black arrow) is noted in the peripheral margin of the mass on the computed tomography scan; E: Section shows spindle-shaped Schwann cells with brownish pigments, psammoma bodies (hematoxylin and eosin, × 100); F: Positive immunoactivity for S-100 protein that are characteristic features of psammomatous melanotic schwannoma (× 100).

Case 2: The adhesion between the mass and spinal cord was severe and bleeding was severe so only a biopsy was performed. Total removal of the mass was not performed.

OUTCOME AND FOLLOW-UP

Case 1: After the surgery, the preoperative symptoms including low back pain and paresthesia in both lower legs were all improved. The patient declined follow-up MRI; however, no special symptoms or signs have since developed.

Case 2: The lesion was followed up three times on MRI once a year after surgery. The size and imaging characteristics of the lesion did not change significantly. Also, an annual chest and abdominal CT exam revealed that there was no evidence of distant metastasis through the follow-up period.

DISCUSSION

A MMNST is composed of Schwann cells capable of melanogenesis[1]. It usually arises in association with spinal or visceral autonomic nerves[5]. Approximately 50% of cases are associated with the Carney complex[7]. Psammomatous MMNSTs account for approximately half of all MMNSTs, and approximately half of these are associated with the Carney complex[8]. Thus, in cases of an MMNST, it is necessary to search for clinicopathologic components of the Carney complex[9]. The Carney complex is characterized by autosomal dominant inheritance as well as familial multitumoral syndrome, comprising myxomas (cardiac, cutaneous and mammary), spotty pigmentation and endocrine overactivity (Cushing’s syndrome and acromegaly)[2]. However, in our case, neither patient had clinical or physical findings or a family history of the Carney complex.

Solomou et al.[10] reviewed 65 reported cases of extramedullary spinal melanotic schwannoma and these tumors most commonly occurred between 30 years and 40 years of age. But in our two cases, it was diagnosed at a much older age. MMNST patients usually have symptoms due to compression of
adjacent structures during the fourth decade. A previous literature review revealed that more than 50% of cases have local recurrence or distant metastasis or both[10]. However, in the present cases, malignant changes, local recurrence and metastases were not detected. There are no known diagnostic radiological characteristics for MMNSTs; therefore, it is sometimes difficult to distinguish them from other melanin-containing tumors. On CT, a psammomatous MMNST can appear as a dense mass with calcification. In this situation, calcified meningioma, which is common in this location, should be included in the differential diagnosis. On MRI, MS of the spine is usually located along the spinal nerve root and sometimes in the form of a dumbbell[11]. Since our cases were located in the intradural space, the dumbbell shape was not visible. MMNSTs rarely occur within the spinal cord. In our second case, the mass lesion had an eccentric position within the spinal cord.

The presence of paramagnetic free radicals in melanin produces characteristic T1 hyperintensity and T2 hypointensity in tumors, providing important clues regarding the more specific properties of what might appear as a typical neuron-enveloping tumor. This T1 hyperintensity is a hallmark of melanin, but subacute bleeding can also explain these findings, and it can be difficult to distinguish them from hemorrhagic lesions such as spongy malformations[12]. Melanin-containing lesions, including malignant melanoma, melanoma, pigmented neurofibroma, perineural melanoma and metastatic melanoma are another reason for T1 shortening[7]. The signal intensity of the lesion may be variable due to the concentration of melanin[13]. They usually show enhancement with contrast.

Although complete resection is sufficient to treat sporadic and psammomatous types of MMNST, malignant deformation and recurrence of the tumor should always be kept in mind and subsequent imaging of the patient should continue for at least 5 years[14]. In case 1, complete excision of the mass was possible; but in case 2, the adhesion between the mass and spinal cord was severe so only a biopsy was performed. No imaging features enable differentiation between MMNST and conventional schwannomas. In addition, the differentiation between intradurally-located melanotic tumors and other intradural tumors in the spine is difficult. The differential diagnosis of MMNSTs of apparent nerve sheath origin includes leptomeningeal melanocytoma, ancient schwannoma, pigmented neurofibroma, biphasic synovial sarcoma, neurilemoma and melanoma[7].

Case 1 was characterized by the location of the mass near the conus medullaris and calcification at the peripheral rim of the mass. Thus, calcified meningioma and myxopapillary ependymoma were included in the differential diagnosis. Although previous reports revealed various locations of spinal MMNSTs[10], we didn’t consider an MMNST with a psammomatous body as a differential diagnosis. Punctate calcification foci are frequently found in spinal meningiomas due to the psammoma bodies[15].
conventional schwannomas usually demonstrate a higher signal intensity on T2WI, cystic changes and inhomogeneous enhancement. In our case, the tumor showed T1 hyperintensity and T2 hypointensity so we didn’t consider the possibility of these rare variants of nerve sheath tumor. Although the MR findings in myxopapillary ependymomas were nonspecific, the diagnosis can be suggested by a large, intensely enhancing, intradural extramedullary thoracolumbar mass that extends for several vertebral levels[16]. Intradural extramedullary lesions in the region of the conus medullaris include myxopapillary ependymoma, paraganglioma, nerve sheath tumor, meningioma and metastasis[16]. Due to the older age and uncommon location (conus medullaris) compared to previous reports[10], the correct diagnosis was difficult in case 1.

In case 2, the high signal intensity on T1WI and low signal intensity on T2WI of the mass were characteristic. Thus, melanoma and angioma were included in the differential diagnosis. The majority of spinal melanomas are frequently observed in the middle or lower thoracic spinal cord. Liu et al[17] showed a pattern of spinal melanoma on MRI which includes hyperintensity on T1WI and iso- or hypointensity on T2WI. Compared to melanotic schwannoma, spinal melanoma contains more concentration of melanin[10]. Melanoma does not always show a homogeneous pattern on MRI[18]. The MRI signal of melanocytic tumors depends on the presence of melanin, acute or chronic intratumoral hemorrhages and fat deposits. On the other hand, cavernous angiomas exhibit a dark rim on T2WI due to hemosiderin deposition[19]. Small size, eccentric axial location, minimal enhancement and absence of edema are significant MR findings of cavernous angioma[19]. In addition, longitudinal spreading of hemorrhage may be observed on serial follow-up images of spinal cavernous angiomas[19].

Considering previous reports, case 2 shows relatively characteristic findings of an MMNST, but older age and the rarity of this disease entity made the correct diagnosis difficult. However, unlike in case 1, the patient in case 2 undertook diffusion-weighted images. Most hypercellular malignant tumors show diffusion restriction, but our case did not show any diffusion restriction. Considering the malignant behavior of this rare disease, future studies could focus on functional images that could predict recurrence or metastasis of this disease.

**CONCLUSION**

In conclusion, we report on two cases of melanotic schwannoma located in the intradural space of the spine. The two MMNSTs reported here had rare intradural locations and showed various characteristics of relatively common tumors that could have an intradural location such as meningioma, schwannoma, melanoma and angioma. They also developed at an older age than in the cases previously reported in the literature. When calcification is seen in a mass, MMNST, as well as meningioma, should be considered among psammomatous type tumors in the differential diagnosis. Moreover, when the mass exhibits a characteristic signal intensity suggesting melanin-like T1 hyperintensity with T2 hypointensity, MMNST may be included in the differential diagnosis.

**FOOTNOTES**

**Author contributions:** Song YS and Yeom JA contributed to manuscript writing, editing and data collection; Choi KU and Han IH contributed to data analysis; Lee IS contributed to conceptualization and supervision; All authors have read and approved the final manuscript.

**Supported by** a Clinical Research Grant from Pusan National University Hospital (2020).

**Informed consent statement:** Informed written consent was obtained from the patients for publication of this report and any accompanying images.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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REFERENCES


17 Liu QY, Liu AM, Li HG, Guan YB. Primary spinal melanoma of extramedullary origin: a report of three cases and systematic review of the literature. Spinal Cord Ser Cases 2015; 1: 15003 [PMID: 28053708 DOI: 10.1038/scsandc.2015.3]


When should endovascular gastrointestinal anastomosis transection Glissonean pedicle not be used in hepatectomy? A case report

Jian Zhao, Yan-Li Dang

Abstract

BACKGROUND
The literature on post-hepatectomy bile duct injury (PHBDI) is limited, lacking large sample retrospective studies and high-quality experience summaries. Therefore, we reported a special case of iatrogenic bile duct injury caused by Glissonean pedicle transection with endovascular gastrointestinal anastomosis (endo-GIA) during a right hepatectomy, analyzed the causes of this injury, and summarized the experience with this patient.

CASE SUMMARY
We present the case of a 66-year-old woman with recurrent abdominal pain and cholangitis due to intrahepatic cholangiectasis (Carolii's disease). Preoperative evaluation revealed that the lesion and dilated bile ducts were confined to the right liver, with right hepatic atrophy, left hepatic hypertrophy, and hilar translocation. This problem can be resolved by performing a standard right hepatectomy. Although the operation went well, jaundice occurred soon after the operation. Iatrogenic bile duct injury was considered after magnetic resonance cholangiopancreatography review, and the second operation were performed 10 d later. During the second operation, it was found that the endo-GIA had damaged the lateral wall of the hepatic duct and multiple titanium nails remained in the bile duct wall. This led to severe stenosis of the duct wall, and could not be repaired. Therefore, the injured bile duct was transected, and a hepatic-jejunal-lateral Roux-Y anastomosis was performed at the healthy part of the left hepatic duct. After this surgery, the patient had a smooth postoperative recovery, and the total bilirubin gradually decreased to normal. The patient was discharged 41 d after operation. No anastomotic stenosis was found at the 6 mo of follow-up.

CONCLUSION
Not all cases are suitable for endo-GIA transection of Glissonean pedicle,
especially in cases of intrahepatic bile duct lesions. PHBDI caused by endo-GIA is very difficult to repair due to extensive ischemia, which requires special attention.

**Key Words:** Endovascular gastrointestinal anastomosis; Glissonean pedicle; Hepatectomy; Bile duct injury; Safety; Case report

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**Core Tip:** There have been few reports on post-hepatectomy bile duct injury (PHBDI). In this report, we present a case of PHBDI caused by the wrong choice of transection tool, such as endovascular gastrointestinal anastomosis (endo-GIA), which was successfully saved by reoperation. We wanted to draw attention to the fact that not all cases are suitable for endo-GIA transection of Glissonean pedicle.

**Citation:** Zhao J, Dang YL. When should endovascular gastrointestinal anastomosis transection Glissonean pedicle not be used in hepatectomy? A case report. *World J Clin Cases* 2022; 10(24): 8742-8748

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i24/8742.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i24.8742

**INTRODUCTION**

There have been more reports on iatrogenic bile duct injuries (BDIs) after laparoscopic cholecystectomy (LC), i.e., LCBDIs, although its incidence has been reduced to 0.3%-0.7%[1]. However, the incidence of post-hepatectomy bile duct injury (PHBDI) is as high as 3.6%-17%[2], accounting for one-third of the post-hepatectomy mortality[3], and more attention should be paid to this type of injury to decrease its occurrence[4]. With the increasing popularity of laparoscopic and robotic hepatectomy worldwide[5,6] and the increasing reliance on the use of energy devices and Tric-staple™, as well as the difficulty in determining the spatial relationship between catheters due to the lack of complete stereoscopic vision and tactile feedback in the laparoscopic field of vision, the true incidence of PHBDI may be higher[7]. However, there is still a lack of large sample clinical studies and high-quality experience summaries specifically for its cause analysis and prevention strategies. Thus, we reported a specific case of PHBDI caused by Glissonean pedicle transection with endovascular gastrointestinal anastomosis (endo-GIA) during right a hemi-hepatectomy, analyzed its causes, and summarized the experience with this patient.

**CASE PRESENTATION**

**Chief complaints**
A 66-year-old Chinese female presented with recurrent abdominal pain for 20 years and fever for 1 wk.

**History of present illness**
The patient began to experience intermittent dull pain in the upper abdomen more than 20 years ago, with no obvious inducement, and spontaneously relieved by rest. Initially, no other concomitant symptoms were found, but the pain occurred 1-2 times per month. In the past 2 years, the frequency of abdominal pain increased to about 1-2 times a week. The patient developed chills and a fever 1 wk ago, with the highest body temperature of 38.3 °C, which were relieved after oral administration of antipyretic and analgesic drugs. No jaundice was evident.

**History of past illness**
The patient was diagnosed as type 2 diabetes and hypertension 2 years ago, which has been controlled well with oral medication.

**Personal and family history**
The patient had no special personal and family history.

**Physical examination**
At admission, the patient’s consciousness was clear, with a body temperature of 37.3 °C, and a blood pressure on 145/85 mmHg, without skin and sclera jaundice. The abdomen was soft and flat, with percussive pain in the right upper quadrant and liver area, without tenderness or rebound pain.
Murphy’s sign was negative.

**Laboratory examinations**

Laboratory tests indicated that only alkaline phosphatase and gamma-glutamyltransferase (γ-GTP) were slightly elevated at admission, with normal infection indicators, tumor markers, and total bilirubin (TBIL) (Table 1).

**Imaging examinations**

Contrast-enhanced abdominal magnetic resonance imaging demonstrates a dilated bile duct in right liver with a large cyst occupying the beginning of the right anterior and posterior hepatic ducts, accompanied by rights liver atrophy, left liver hyperplasia, and counterclockwise hilar translocation (Figure 1A and B). The opening of left hepatic duct was very close to the cyst (Figure 1C), the right portal vein branch was not clearly seen, with no variation of extrahepatic bile duct and other blood vessels (Figure 1D and E). The peripheral bile ducts were full of stones (Figure 1F). According to the preoperative imaging evaluation, standard right hepatectomy could resolve this lesion.

**FINAL DIAGNOSIS**

According to clinical and imaging features, intrahepatic cholangiectasia (Caroli’s disease, Todani type-V) with recurrent cholangitis, atrophy-hypertrophy complex, and hilar translocation was considered.

**TREATMENT**

After preoperative evaluation, it was considered that the lesion was confined to the right liver and could be resolved by standard right hepatectomy, so the first operation was performed. During the operation, obvious fibrosis and atrophy were found in the right liver (Figure 2A). The diseased bile duct was close to the bifurcation of the left and right hepatic ducts, and the extrahepatic bile duct was slender. The initial part of the right hepatic duct was first separated from extrasheathical dissection method, the right hepatic duct was then transected with endo-GIA (Figure 2B and C), and finally a standard right hepatectomy was performed along the demarcation line of the liver surface. No abnormalities were found during the operation. Postoperative reexamination found a gradual increase in TBIL, but there were no significant change in white blood cells (Table 1), and the patient did not complain of any special uncomfortable feeling. Magnetic resonance cholangiopancreatography (MRCP) was reexamined on the 5th postoperative day and no extrahepatic bile duct was found, and the left hepatic duct was dilated compared with the operation before (Figure 2D). At this point, we realized that a biliary tract injury had occurred, so a second operation was performed on the 10th day. During the second operation, the lateral wall of the hepatic duct damaged by endo-GIA was found, which had led to severe stenosis and occlusion. Residual titanium nails could be seen in the damaged bile duct wall, leading to locally significant inflammatory edema and ischemia (Figure 2E and F). The damage was about 4 cm long, which could not be repaired at this location. The portal vein and the hepatic artery were not damaged. Therefore, the injured hepatic duct was directly transected, the main trunk of the left hepatic duct was dissected and exposed, and the left hepatic duct and jejunum side-by-side anastomosis (Roux-Y anastomosis) was completed (Figure 2G). The patient recovered smoothly, and no additional complications occurred after re-operation. TBIL and γ-GTP levels gradually decreased, and liver function gradually improved (Table 1). Postoperative pathology found chronic inflammation of the bile duct wall, but no malignant cells were found (Figure 2H). The patient was discharged on the 41st day after operation.

**OUTCOME AND FOLLOW-UP**

After half a year of follow-up, the patient had no abdominal pain or fever, no anastomotic stenosis, and normal liver functions. The patient was later lost due to coronavirus disease 2019 pandemic.

**DISCUSSION**

Iatrogenic bile duct injury is a permanent pain for hepatobiliary surgeons[8]. However, the understanding of BDI is often limited to LCBDI, rather than PHBDI, as few scholars pay attention to this injury. Both injuries have significant differences in injury causes, risk factors, injury characteristics, clinical classification, preventive principles, and treatment methods[4]. The reviews of the literature on
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Table 1 Laboratory findings

<table>
<thead>
<tr>
<th></th>
<th>On admission</th>
<th>Day 3 postoperatively</th>
<th>Day 8 postoperatively</th>
<th>Day 13 postoperatively (day 3 after re-operation)</th>
<th>Day 35 postoperatively (day 25 after re-operation)</th>
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<tr>
<td>WBC (× 10^9/L)</td>
<td>4.53</td>
<td>12.81</td>
<td>13.21</td>
<td>16.3</td>
<td>6.41</td>
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<tr>
<td>Hb (g/dL)</td>
<td>13.2</td>
<td>11.9</td>
<td>12.9</td>
<td>12</td>
<td>13.5</td>
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<tr>
<td>Plt (× 10^9/L)</td>
<td>210</td>
<td>243</td>
<td>288</td>
<td>179</td>
<td>231</td>
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<tr>
<td>TBIL (μmol/L)</td>
<td>17.6</td>
<td>68</td>
<td>158.7</td>
<td>135.1</td>
<td>15.6</td>
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<tr>
<td>AST (U/L)</td>
<td>17</td>
<td>891</td>
<td>780</td>
<td>860</td>
<td>14</td>
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<tr>
<td>ALT (U/L)</td>
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<td>706</td>
<td>612</td>
<td>778</td>
<td>13</td>
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<tr>
<td>γ-GTP (U/L)</td>
<td>84</td>
<td>349</td>
<td>694</td>
<td>589</td>
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<tr>
<td>ALP (U/L)</td>
<td>75</td>
<td>344</td>
<td>481</td>
<td>450</td>
<td>57</td>
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<tr>
<td>Alb (g/dL)</td>
<td>42.4</td>
<td>34.5</td>
<td>31.6</td>
<td>29.7</td>
<td>39.6</td>
</tr>
<tr>
<td>Cr (μmol/L)</td>
<td>65.1</td>
<td>58</td>
<td>38.6</td>
<td>31.5</td>
<td>68</td>
</tr>
<tr>
<td>PT (s)</td>
<td>10.2</td>
<td>11.5</td>
<td>14.6</td>
<td>13.1</td>
<td>9.8</td>
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<tr>
<td>CRP (mg/L)</td>
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<td>89.1</td>
<td>135.7</td>
<td>171.6</td>
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<tr>
<td>CA19-9 (μ/mL)</td>
<td>17.7</td>
<td></td>
<td></td>
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<td>CEA (ng/mL)</td>
<td>2.3</td>
<td></td>
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</table>

Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CA19-9: Carbohydrate antigen19-9; CEA: Carcinoembryonic antigen; Cr: Creatinine; CRP: C-reactive protein; γ-GTP: Gamma-glutamyltransferase; Hb: Hemoglobin; Plt: Platelets; PT: Prothrombin time; TBIL: Total bilirubin; WBC: White blood cells.

the clinical characteristics of PHBDI show that it mostly occurs to the high bile duct (the confluence of the left and right hepatic ducts and above) and is prone to vascular injury[9-10]. Injuries to laparoscopic hepatectomy are often related to the use of endo-GIA/Endo-Cutter, and energy equipment, with difficult repair and poor prognosis[9]. Clinical manifestations are hyperbiliary stenosis, obstruction, bile duct leakage, and bile duct bleeding. Most patients, already complicated with basic liver diseases (cirrhosis, cholangitis, liver cancer, etc.), can develop severe abdominal infection, liver failure, and even death[11].

The causes of the injury in our patient are various, including objective unfavorable factors, such as the lesion duct’s location close to the reserved side bile duct and right liver atrophy leading to hilar translocation. However, the root cause of this case was the wrong choice of transection tools, such as endo-GIA, rather than the wrong process when using it. Initially, during the operation, the author and assistants repeatedly remind each other not to accidentally hurt the healthy side bile duct, and therefore, the injury was not likely caused by carelessness. Second, because the lesion bile duct of cystic dilation was too close to the common hepatic duct, there was no “safe boundary” when it was transected. Because endo-GIA’s fuselage itself has a certain width, the tissue inside this objectively small width is invisible when transected. Predictably, in this particular type of case, if endo-GIA is used to transect the Glissonean pedicle, it is expected that there is a higher chance that BDI will occur. This is the contradiction between “removal of lesions thoroughness” and “surgical safety”.

Therefore, the important points that we learned from this particular case include: (1) It is necessary to transect the Glissonian pedicle in or as close as possible to the liver, whether the Glissonian pedicle extrahepatic or intrahepatic dissection technology is adopted[13-15]; (2) Endo-GIA should not be selected for transection of the Glissonian pedicle in hepatectomy cases involving intrahepatic bile duct diseases, as we need to treat the intrahepatic bile duct separately to prevent the bile duct injury. It should not be recommended for cases such as intrahepatic cholangiectasia, intrahepatocholedochal stones,
Figure 1 Preoperative clinical image of the abdomen. A: The right liver atrophy and compensatory hypertrophy of the left liver were seen, with the hepatic fissure (the white arrow) transposed to the right; B: Right hepatic duct cystic dilatation; C: The opening of left hepatic duct (the white arrow) is very close to the cyst; D: The red line shows the expected excision line and the blue arrows show the three major hepatic veins; E: No vascular variation was found and the left portal veins were also transposed to the right; F: Magnetic resonance cholangiopancreatography was used to evaluate intrahepatic and extrahepatic bile ducts. The end of the right hepatic duct is full of stones (the white arrow). LHV: Left hepatic vein; MHV: Middle hepatic vein; P3: Portal vein of Segment 3; P5: Portal vein of Segment 5; RHV: Right hepatic vein.

CONCLUSION
Not all cases are suitable for endo-GIA transection of the Glissonean pedicle, especially in cases of intrahepatic bile duct lesions. PHBDI caused by Endo-GIA is very difficult to repair due to extensive ischemia, which requires special attention.
Figure 2 Postoperative clinical images and surgical schematic diagram. A: The right liver atrophy and left liver hyperplasia were confirmed intraoperatively. The area within the yellow line is the right liver with fibrosis and atrophy; B: The portal vessels were dissected, and there was no variation in extrahepatic vessels; C: The right hepatic duct was transected by endovascular gastrointestinal anastomosis from its origin; D: Postoperative magnetic resonance cholangiopancreatography reexamination showed that the extrahepatic bile duct was not shown; E: Severe ischemia (the yellow area) was found due to titanium nail damage to the lateral wall of the hepatic duct during the reoperation exploration. The anastomosis of the left hepatic duct (the white arrow) was suspended by silk thread; F: Schematic diagram of the causes of bile duct injury; G: Schematic diagram of the side-by-side anastomosis of the hepatic duct and jejunum; H: Postoperative pathology (× 100) showed chronic inflammation of the bile duct wall, and no malignant cells were found. 1L: Bile duct of Segment 1L; B2: Bile duct of Segment 2; B3: Bile duct of Segment 3; B4a: Bile duct of Segment 4a; CBD: Common bile duct; GB: Gall bladder; IVC: Inferior vena cava; LPV: Left portal vein; PV: Portal vein.

ACKNOWLEDGEMENTS

The authors thank Dr. Dang YL, Department of Obstetrics, The First People’s Hospital of Yunnan Province, for participating in the discussion and conclusion.

FOOTNOTES

Author contributions: Zhao J and Dang YL designed this report; Zhao J wrote the paper.

Supported by Basic Research Foundation of Yunnan Province, No. 202101AY070001-282.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report.

Conflict-of-interest statement: The authors declare that they have no competing interests.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).
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REFERENCES


VARS2 gene mutation leading to overall developmental delay in a child with epilepsy: A case report

Xiao-Hui Wu, Shuang-Zhu Lin, Yan-Qiu Zhou, Wan-Qi Wang, Jia-Yi Li, Qian-Dui Chen

BACKGROUND
The mitochondrial respiratory chain defects have become the most common cause of neurometabolic disorders in children and adults, which can occur at any time in life, often associated with neurological dysfunction, and lead to chronic disability and premature death. Approximately one-third of patients with mitochondrial disease have biochemical defects involving multiple respiratory chain complexes, suggesting defects in protein synthesis within the mitochondria. We here report a child with VARS2 gene mutations causing mitochondrial disease.

CASE SUMMARY
A girl, aged 3 years and 4 mo, had been unable to sit and crawl alone since birth, with obvious seizures and microcephaly. Brain magnetic resonance imaging showed symmetrical, flaky, long T1-weighted and low T2-weighted signals in the posterior part of the bilateral putamen with a high signal shadow. T2 fluid-attenuated inversion recovery imaging showed a slightly high signal and diffusion-weighted imaging showed an obvious high signal. Whole-exome gene sequencing revealed a compound heterozygous mutation in the VARS2 gene, c.1163(exon11)C>T and c.1940(exon20)C>T, which was derived from the parents.
The child was diagnosed with combined oxidative phosphorylation deficiency type 20.

**CONCLUSION**
In this patient, mitochondrial disorders including Leigh syndrome and MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) were ruled out, and combined oxidative phosphorylation deficiency type 20 was diagnosed, expanding the phenotypic spectrum of the disease.

**Key Words:** Mitochondrial aminoacyl-tRNA synthetase; Mitochondrial diseases; \textit{VARS2}; Case report

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**Core Tip:** The clinical manifestation of the child was remarkable. Through the comprehensive analysis of symptoms, physical examination, biochemical examination and gene sequencing, the child was confirmed to have combined oxidative phosphorylation deficiency type 20, and the phenotypic spectrum of the disease was thus expanded.

**Citation:** Wu XH, Lin SZ, Zhou YQ, Wang WQ, Li JY, Chen QD. \textit{VARS2} gene mutation leading to overall developmental delay in a child with epilepsy: A case report. \textit{World J Clin Cases} 2022; 10(24): 8749-8754
**URL:** https://www.wjgnet.com/2307-8960/full/v10/i24/8749.htm
**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i24.8749

**INTRODUCTION**
Mitochondrial disorders include widely heterogeneous clinical syndromes, frequently presenting as encephalomyopathy and/or cardiomyopathies, associated with a broad range of causative genes\cite{1,2}. Their biochemical signature is the presence of defective activity in the mitochondrial respiratory chain complexes, resulting in faulty oxidative phosphorylation (OXPHOS), which can impair ATP production. Mutations in several genes associated with defects of mitochondrial protein synthesis, affecting either mitochondrial DNA (mtDNA) or nucleus-encoded genes, have been reported in a range of mitochondrial syndromes\cite{3}.

In recent years, an increasing number of mitochondrial diseases have been associated with mutations in the mitochondrial aminoacyl-tRNA synthetase, a key enzyme for mitochondrial protein synthesis\cite{4}. Mutations in this enzyme have also been associated with diverse clinical presentations, usually inherited as early-onset autosomal recessive traits. The synthesis of mitochondrial proteins involves complex interactions between mtDNA-encoded RNA and nuclear DNA-encoded proteins, such as elongation factors, ribosomal proteins, and aminoacyl-tRNA synthetase. Among the 17 mitochondria-specific aminoacyl-tRNA synthases, \textit{VARS2} encodes the mitochondrial valine-tRNA synthase, a class I enzyme that catalyzes the attachment of a valine to its cognate tRNA molecule in a highly specific reaction\cite{5}.

Bruni et al\cite{4} studied 13 patients with \textit{VARS2} gene mutations from different families, the clinical manifestations are severe cerebral myopathy and cardiomyopathy at birth. Features include hypotonia, psychomotor delay, feeding difficulties, cranial magnetic resonance imaging (MRI) abnormalities, and elevated lactate levels.

**CASE PRESENTATION**

**Chief complaints**
A girl aged 3 years and 4 mo, was admitted to Quanzhou Children’s Hospital on July 14, 2021 due to three convulsions in a day.

**History of present illness**
Her convulsions occurred on the day of admission and manifested as eyes staring rightward, mouth tilted to the right, clonic twitching of the right limbs, and loss of consciousness. Each convolution lasted ~20 min and relieved after Anticonvulsant therapy with diazepam without fever or vomiting.
History of past illness

The child’s weight at birth was 3.3 kg and height was 50 cm. Intellectual and motor development was retarded after birth. She could track using her eyes and responded to voices at 3 mo. She could hold her head up steadily at 5 mo, turn over to the prone position, and could say “eee, eee, eee, eee”. At 7 mo, she could take the initiative and reach out to grab objects. At almost 1 year old she could turn over freely, but at 13 mo could still not sit alone, crawl or stand alone; she could move objects from one hand to the other, but could only make “babbling” vocalizations, and she underwent short-term rehabilitation training. By the age of 3 years and 4 mo, she still could not sit alone, crawl or stand alone; she could move objects from one hand to the other, but could only say “papa, mama, nana”.

Personal and family history

The child is the third child and the second birth (the first led to abortion), and was delivered vaginally at 39 + 4 wk of gestation. The parents denied a history of intrauterine hypoxia and birth asphyxia, and the mother was 43 years old, healthy during pregnancy and denied taking medicine, with no history of poisoning. The parents and older brother were healthy, with no family history of epilepsy, and psychomotor retardation.

Physical examination

The child’s head circumference was 47 cm, height 95 cm, and weight 12 kg, with no special facial features, clear consciousness, good spirit, no café-au-lait spots or depigmentation on the entire skin, no neck resistance, clear breath sounds in both lungs, and no dry or wet rales. Her heart rate was 116 bpm, the heart rhythm was consistent, heart sounds were strong, no murmur was heard, the abdomen was soft, and no masses were palpable. The liver and spleen were unpalpable, and muscle strength of the limbs could not be determined. The muscle tone in the limbs was increased, bilateral ankle joint contractures, knee tendon reflexes were active and symmetrical, and the Brudzinski sign was negative bilaterally.

Laboratory examinations

Auditory evoked potential (April 10, 2019) showed that the bilateral auditory brainstem-evoked potential results were normal and the critical bilateral V/I (ratio of the highest and lowest potential) peak ratios were 0.67 for the left ear and 0.68 for the right ear, and the normal bilateral threshold was 30 dBnHL.

Urine filter paper organic acid detection and analysis (April 10, 2019) showed no abnormalities.

TORCH examination (including toxoplasma, cytomegalovirus and herpes simplex virus) IgM was negative (April 12, 2019).

Blood tandem mass spectrometry analysis (April 28, 2019) showed that C5OH (0.84) and the ratio of ion mass to charge were still elevated, and that blood ammonia, liver function, blood gas, lactic acid, and urine organic acid had improved. Gene analysis was planned to exclude 3-methylcrotonyl-CoA hydroxylation enzyme deficiency and perhydroxylase/biotinidase deficiency.

Genetic testing with trio whole exome sequencing (April 29, 2019) showed the following: (1) Chromosomal aneuploidy; the chromosome composition was 46, XX, and the number of chromosomes was normal; and (2) Chromosome microdeletion or microduplication was negative. No clinically identifiable pathogenic copy number variations were found within the scope of this assay.

Thyroid function tests (August 19, 2019) showed that triiodothyronine (T3), thyroxine (T4), free T3, free T4 and thyroid-stimulating hormone were normal.

Color Doppler echocardiography (August 19, 2019) showed that the intracardiac structure and cardiac function were normal.

Blood ammonia (July 15, 2021) was normal at 21 μmol/L.

Electroencephalography (July 15, 2021) was abnormal. Each lead in the wake–sleep phase showed diffuse 2-4 Hz mixed spread activity, basically symmetrical in left and right, with no obvious dominant rhythm in the occipital region in the waking period and no typical peaks in the sleep period. The sleep spindle was affected, and the sleep cycle was not easy to identify.

Electromyography (July 31, 2019) showed peripheral nerve damage (motor fiber involvement) in both upper extremities, which was most severe in the left upper extremity.

Imaging examinations

Brain MRI (April 3, 2019) showed symmetrical, patchy, long T1-weighted (Figure 1A) and low T2-weighted (Figure 1B) high signal shadow in the posterior part of the bilateral putamen, slightly high signal on T2 fluid-attenuated inversion recovery (Figure 1C) and an obvious high signal on diffusion-weighted imaging (Figure 1D).

Brain MRI (July 19, 2021) showed bilateral putamen symmetric lesions, and the length and diameter of the lesions were larger than before.
Wu XH et al. VARS2 classic

**FINAL DIAGNOSIS**

The child had clinical characteristics of comprehensive psychomotor developmental delay, microcephaly, seizures, cerebral magnetic brain with obvious symmetrical putamen lesions, and whole exon testing showed compound heterozygous mutations in VARS2 gene (Figure 2), so the child was diagnosed with combined oxidative phosphorylation deficiency 20 (COXPD20).

**TREATMENT**

There is no specific treatment for this disease, and we provided the patient with nutritional supportive care and topiramate to control seizures.

**OUTCOME AND FOLLOW-UP**

During the initial 6-mo follow-up period, the number of seizures decreased, and there was no progression or regression in the psychomotor development of the patient.

**DISCUSSION**

The VARS2 gene contains 30 exons and encodes mitochondrial valine tRNA synthetase, which participates in mitochondrial protein synthesis. Rare biallelic variants in VARS2 are associated with mitochondrial encephalopathy or cardiomyopathy[6]. Mitochondrial disorders are caused by inherited defects of the pyruvate oxidation route. The core of this pathway consists of the OXPHOS system. Components of this system are encoded by the nuclear and the mitochondrial genome. Aside from mitochondrial DNA-encoded tRNAs and rRNAs, the mitochondrial translation apparatus consists of over 100 nuclear-encoded proteins, which are synthesized in the cytoplasm and then imported into the mitochondrial matrix[7].

COXPD20 is an autosomal recessive mitochondrial encephalocardiomyopathy caused by variants in the VARS2 gene located on chromosome 6p21. Presently, there are 17 reported pathogenic variants in the VARS2 gene (https://www.ncbi.nlm.nih.gov/clinvar/?term=VARS2[all])[8].

Our patient aged 3 years and 4 mo, was admitted to hospital due to three convulsions in a day. The clinical presentation of comprehensive development delay and epileptic seizures attracted our attention. We strongly suspected that the child had mitochondrial disease. Nuclear and mitochondrial genes were tested 2 years ago, but the child did not have seizures at that time. Therefore, whole-exon testing was advised again, and in this test, the sequencing depth was increased and a compound heterozygous variant of the VARS2 gene was found. The pathogenicity grade of this variant was uncertain according to the American College of Medical Genetics and Genomics guidelines. But this also led us to confirm a diagnosis of COXPD20, because the biallelic variant of VARS2 is a nuclear gene encoding valine tRNA synthase. Mutations of the VARS2 gene suggest COXPD20 disease. The typical manifestations of that disease include general growth retardation, hypotonia, seizures, and microcephaly.

The patient’s main clinical manifestations were consistent with COXPD20, but unlike the typical disease, the child had increased muscle tone but did not have hypotonia. We did not conduct functional studies of VARS2 gene-associated proteins; thus, we could not determine that the clinical manifestations

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**Figure 1** Brain magnetic resonance images. A: T1; B: T2; C: T2 fluid-attenuated inversion recovery; D: Diffusion-weighted imaging.

DOI: 10.12998/wjcc.v10.i24.8749  Copyright ©The Author(s) 2022.
Figure 2 Whole-exome gene sequencing revealed a compound heterozygous mutation in the VARS2 gene which was derived from the parents. A-C: VARS2: c.1163(exon11)C>T: Proband (A); Father of the proband (B); Mother of the proband (C); D-F: VARS2: c.1940(exon20)C>T: Proband (D); Father of the proband (E); Mother of the proband (F).

were caused by mutations in the VARS2 gene. We considered the possibility of other mitochondrial diseases, including Leigh syndrome and MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) during the course of clinical diagnosis and treatment of this patient, but the clinical presentation of the patient and the results of laboratory tests ruled out the possibility of both diseases.

CONCLUSION

The VARS2 gene is one of the genes encoding mitochondrial aminoacyl-tRNA synthetase. Few patients with VARS2 deficiencies have been described with specific phenotypes. The phenotypes are present at any time during life and demonstrate clinical heterogeneity[9]. We will continue to monitor the patient’s disease changes and conduct related protein function studies if conditions permit.

ACKNOWLEDGEMENTS

We would like to thank the child and her family members for their contributions to this report.
FOOTNOTES

Author contributions: Wu XH is the deputy chief physician of Quanzhou Children’s Hospital where the child was treated, was the main provider of this case; Lin SZ and Zhou YQ reviewed literature, and wrote and revised the manuscript; Wang WQ, Li JY and Chen QD compiled the literature review, conducted the preliminary translation of the report and the subsequent submission; All authors issued final approval for the version to be submitted.

Informed consent statement: Informed consent has been obtained from the children and the parents and we are very grateful to the children and the parents for their contribution to our report.

Conflict-of-interest statement: There is no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

REFERENCES


Junctional bradycardia in a patient with COVID-19: A case report

Abdullah Ibrahim Aedh

Abstract

BACKGROUND
Cardiac arrhythmias, including bradyarrhythmias, have been described as manifestations of coronavirus disease 2019 (COVID-19). Herein, we present a case of junctional bradycardia secondary to possible sinus node dysfunction in a patient with COVID-19.

CASE SUMMARY
The patient was a 32-year-old woman with no significant medical history. On the third day of hospitalization, she developed junctional bradycardia while being hemodynamically stable. The episodes of nodal dysrhythmia with a low heart rate persisted for the next few days and were associated with elevated levels of systemic inflammatory markers. The patient received antiviral and anti-inflammatory treatments for the viral infection but no antiarrhythmic medications. She had a normal sinus rhythm on day 12.

CONCLUSION
Cardiac rhythm monitoring, focusing on the association between cardiac arrhythmias and the systemic inflammatory response, is important in COVID-19 patients.

Key Words: Bradycardia; Case report; COVID-19; Heart rate; SARS-CoV-2; Sinus node dysfunction

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A core tip: A variety of cardiovascular manifestations of COVID-19 have been described. Among these, bradyarrhythmias should be considered one of the main complications and clinical features of COVID-19. Herein, we present a case of junctional bradycardia in a patient with COVID-19. Bradyarrhythmias in COVID-19 patients have been linked to increased systemic inflammatory response and the subsequent dysfunctioning of the sino-atrial node. The inflammatory biomarker and cardiac rhythm monitoring should be considered in patients with COVID-19 during different stages of care.

Case presentation

Chief complaints
A patient presented with chief complaints of headache, sore throat, dry cough, and fever for 3 d.

History of present illness
A 32-year-old female presented with complaints of headache, sore throat, dry cough, and fever for 3 d. On presentation, the patient also complained of bone ache, fatigue, and malaise.

History of past illness
The patient had no significant past medical history.

Personal and family history
There was no family history of heart rhythm disorders.

Physical examination
The patient's physical examination revealed typical vital signs except for a body temperature of 38.9°C. The patient was hemodynamically stable and was not receiving any atrioventricular (AV) node blocking medications.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and was declared a pandemic in March 2020 by the World Health Organization (WHO) [1]. Patients with COVID-19 have had various cardiovascular consequences throughout the pandemic, including acute cardiac damage, myocardial infarction, cardiogenic shock, acute congestive heart failure, and cardiac arrhythmias [2].

Bradyarrhythmia has been identified as a cardiac manifestation of COVID-19 in several studies. In a retrospective case series, Amaratunga et al [3] reported sinus bradycardia in four patients. These episodes lasted for 14 d. Transient sinus bradycardia may be a possible manifestation of COVID-19, and its development may be indicative of the onset of a severe cytokine storm. In another case series, severe bradyarrhythmias were reported in seven patients with COVID-19. The patients had or developed severe bradyarrhythmias during hospitalization and required pacing assistance. None of the patients had pre-existing cardiac diseases. Inflammatory marker levels were significantly elevated in all patients [4]. In another report, new-onset sinus bradycardia resulting from sinus node dysfunction in two elderly patients with COVID-19 was described by Peigh et al [5]. Both patients had persistent sinus bradycardia 2 wk after the onset of sinus node dysfunction. In a recent report from the United Arab Emirates, electrocardiogram (ECG) of a 36-year-old patient with COVID-19 revealed a junctional rhythm with atrial escape capture beats. A Holter study confirmed sinus node dysfunction with frequent pauses of the sinus node block alternating with sinus node arrest [6]. In a case series from India, bradyarrhythmias were reported in seven patients with COVID-19. Complete heart block was noted in five patients. Additionally, sick sinus syndrome was reported in two patients. Four of these patients had ventricular escape beats, and the remaining three had a junctional escape rhythm [7]. Herein, we describe a case of a patient with COVID-19 who developed junctional bradycardia.
Laboratory examinations
Reverse transcription polymerase chain reaction for SARS-CoV-2 using a nasopharyngeal swab confirmed the presence of COVID-19. Laboratory findings revealed lymphopenia with a lymphocyte count of 0.88 × 10³/μL (reference range 1.0–4.0 × 10³/μL), increased C-reactive protein (CRP) levels (95.79 mg/L; reference range < 10 mg/L), high serum ferritin levels (171 μg/L; reference range 12–150 μg/L), and increased D-dimer levels (0.54 mg/L; reference range 0–0.5 mg/L). The patient’s alanine aminotransferase (115.1 U/L; reference range 0–33 U/L) and aspartate aminotransferase (54.8 U/L; reference range 0–0.5 U/L) levels were also elevated. There were no significant electrolyte abnormalities.

At baseline, the patient’s ECG revealed atrial fibrillation with a slow ventricular response accompanied by moderately abnormal T waves. Three days later, the patient developed asymptomatic junctional bradycardia (Figure 1) with a heart rate of 47 beats per minute (BPM) while being awake. Her heart rate further dropped to 38 BPM during sleep. Moderate T wave abnormalities were observed. On day 5 after hospitalization, the ECG again revealed nodal arrhythmia. However, the patient was still asymptomatic and had good mobility and agility. Cardiac enzyme levels were normal, with a creatine kinase level of 48 U/L (reference range 39–308 U/L) and a creatine kinase-MB level of 12.3 U/L (reference range 0–25 U/L). Nodal dysrhythmia with bradycardia persisted for the next 4 days. The patient’s CRP (216.15 mg/L; reference range < 10 mg/L) and D-dimer (0.84 mg/L; reference range 0–0.5 mg/L) levels remained elevated during these episodes and became normal on day 12. Her CRP (4.38 mg/L; reference range < 10 mg/L) and D-dimer (0.36 mg/L; reference range 0–0.5 mg/L) levels coincided with normal sinus rhythm.

Imaging examinations
The patient’s chest computed tomography scan was normal.

FINAL DIAGNOSIS
The presence of clinical symptoms, such as new-onset fever, cough, and fatigue, along with these laboratory findings, are now known manifestations of COVID-19. The patient’s ECG revealed junctional bradycardia.

TREATMENT
After confirmation of the diagnosis, the patient was started on the antiviral drug favipiravir at a dose of 1600 mg twice a day for 1 d, followed by 600 mg twice a day. She was also administered 8 mg of dexamethasone intravenously daily for its anti-inflammatory effects and 40 mg of subcutaneous enoxaparin daily as an anticoagulant. Additionally, the patient received intravenous paracetamol for fever, omeprazole as prophylaxis for gastrointestinal bleeding, and ondansetron for nausea (two doses).

OUTCOME AND FOLLOW-UP
The patient’s symptoms significantly improved over the course of treatment. Besides the episodes of bradycardia, she was doing fine. On day 7, favipiravir was stopped following improvement in patient’s condition. On day 9, she was discharged upon her request with the recommendation of daily ECG monitoring. The patient’s heart rate gradually normalized and ECG on day 12 revealed a normal sinus rhythm (Figure 2). Figure 3 depicted the chronological flowchart of the patient’s treatment course.

DISCUSSION
An array of cardiovascular complications of COVID-19, including cardiac arrhythmias, has been previously reported. However, the mechanisms underlying cardiac involvement in COVID-19 remain poorly understood. Multiple mechanisms may contribute to the development of arrhythmias in these patients. COVID-19 may cause acute bradycardia events by the following mechanisms: direct infiltration of myocardial cells and the conduction system via angiotensin-converting enzyme-2 (ACE2) receptors, aggravation of pre-existing conduction diseases during acute illness, cardiac injury, hemodynamic instability, alteration in the intrinsic cardiac nervous system leading to autonomic dysfunction, a secondary effect of hypoxia caused by pulmonary injury, electrolyte abnormalities, and an enhanced systemic inflammatory response [7-10]. SARS-CoV-2 may also activate the ACE2 receptor by utilizing the spike protein to enter the host cell. This event leads to down-regulation of ACE2 receptors and has been associated with conduction disturbances subsequent to adverse myocardial
The patient developed junctional bradycardia, a slow heart rhythm that originates from the AV node instead of the sinoatrial (SA) node. It can develop from pathology in the SA node causing it to fail as a pacemaker, or from pathology in the AV node, causing it to misfire. While the patient’s cardiac biomarker levels were normal, she had elevated levels of systemic inflammatory markers throughout the arrhythmic events. High levels of inflammatory mediators, such as cytokines, may directly affect the SA node and the conduction system, leading to the development of bradycardia. This event might have been the cause of bradycardia in our patient. Notably, the patient developed junctional bradycardia on day 6 of the illness, which is within the cytokine storm’s onset timetable, similar to the case reported by Amaratunga et al[3].

The incidence of arrhythmias is often associated with disease severity[9,10]. However, in our case, the patient’s condition was not severe and did not require admission to the intensive care unit. The patient did not receive any corrective treatment for bradycardia, as the episodes were asymptomatic and short-lived.

The patient had no pre-existing cardiac conduction abnormalities or structural heart disease, and she was not taking any AV node blocking medications that could have provoked bradycardia. The episodes of bradycardia in our patient may partly result from possible dysfunction of the sinus node by the direct or indirect effect of SARS-CoV-2 and systemic illness on the cardiovascular system.

Drugs used to treat COVID-19 may also contribute to conduction system disturbances[7-10]. Since dexamethasone was first assumed to be the cause of bradycardia, it was stopped on day 3. Dexamethasone was restarted after nodal dysrhythmia with bradycardia persisted from day 5 onwards, along with increased systemic inflammatory markers. In a recent case report from Qatar, favipiravir was attributed to asymptomatic severe sinus bradycardia with a heart rate of 30 BPM in a middle-aged woman. After the drug was stopped, the event resolved[11]. In addition, in the WHO database, bradycardia has been reported as a suspected adverse drug event to favipiravir[12]. However, in our case, the event of junctional bradycardia persisted even after the favipiravir was stopped on day 7 and the patient’s heart rate gradually normalized as her condition improved on day 12 of presentation.
CONCLUSION

Patients with COVID-19 are increasingly presenting with bradyarrhythmias. The specific mechanisms fundamental to the development of bradyarrhythmias in these patients remain indistinct, and they may be multifactorial. The development of bradyarrhythmias can be considered a clinical feature of COVID-19, which could imply cardiac involvement. Therefore, cardiac rhythm monitoring should be performed during therapy, recovery, and discharge and cardiac and inflammatory biomarker monitoring should also be considered.

FOOTNOTES

Author contributions: The author confirms being the sole contributor of this work and has approved it for publication.

Informed consent statement: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict-of-interest statement: The author declares no conflict of interest.

CARE Checklist (2016) statement: The author has read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Zhang H
REFERENCES
Application of 3 dimension-printed injection-molded polyether ether ketone lunate prosthesis in the treatment of stage III Kienböck’s disease: A case report

Cheng-Song Yuan, Yao Tang, Hai-Qiong Xie, Tao-Tao Liang, Hong-Tao Li, Kang-Lai Tang

Specialty type: Orthopedics
Provenance and peer review: Unsolicited article; Externally peer reviewed.
Peer-review model: Single blind

Abstract
BACKGROUND
Polyether ether ketone (PEEK) is a high-performance medical polymer, and there are some clinical cases of PEEK prosthesis implantation. However, application of 3D-printed injection-molded PEEK lunate prosthesis for treatment of stage III Kienböck’s disease has not been reported. This study’s purpose was to analyze the clinical efficacy of 3D-printed injection-molded PEEK lunate prosthesis in the treatment of stage III Kienböck’s disease and thus provide a good therapeutic choice for Kienböck’s disease.

CASE SUMMARY
We report a patient with stage III Kienböck’s disease. With the healthy lunate bone as reference, 3D lunate reconstruction was performed using a mirroring technique. A PEEK lunate prosthesis was prepared by 3D printing and injection molding, and then it was inserted into the original anatomical position after removing the necrotic lunate bone. Wrist pain and function, anatomical suitability of the lunate prosthesis, and complications were evaluated and analyzed postoperatively. At the last visit (one year after surgery), the range of motion, grasp force, visual analog scale score and Cooney score of the affected wrist were significantly improved, and postoperative X-ray examination indicated that the lunate prosthesis had good anatomical suitability for adjacent bony structures.

CONCLUSION
The 3D-printed injection-molded PEEK lunate prosthesis demonstrated definite efficacy in treating stage III Kienböck’s disease.

Key Words: 3D printing; Polyetheretherketone; Kienböck disease; Lunate fixation; Lunate collapse; Clinical outcomes; Case report
Core Tip: Polyether ether ketone (PEEK) has been widely used in the preparation of human bone tissue scaffolds and joint prostheses. This study evaluates the clinical efficacy of 3D-printed injection-molded PEEK lunate prosthesis designed by our team in the treatment of stage III Kienböck’s disease. Compared with other replacement methods, this technique can better reconstruct the anatomical structure of the wrist, alleviate pain, and restore the activity function and grip strength of the patient. Imaging examination confirmed that the lunar bone cement prosthesis has good anatomical adaptability. 3D-printed injection-molded PEEK lunate prosthesis is a safe and effective artificial replacement technique.

INTRODUCTION
Kienböck’s disease is one of the main causes for wrist pain and movement limitation[1]. Stage III Kienböck’s disease is clinically characterized by lunate rupture, necrosis, atrophy and flattening[2], and its treatment aims to conserve normal structure, restore movement function, and relieve wrist symptoms. There are no uniform surgical procedures for Kienböck’s disease, and revascularization, biomechanical therapy, lunate resection and substitute implantation are all commonly used in clinical practice, but they have varying efficacy[3].

Polyether ether ketone (PEEK) is a special thermoplastic polymer, which has the advantages of high strength, high stiffness, corrosion resistance, and hydrolysis resistance. Compared with traditional metal materials, the elastic modulus of PEEK is closer to that of human cortical bone, and it has good plasticity. In the 1990s, as a substitute for metal implants, PEEK was increasingly used in the field of orthopedics. PEEK has good biocompatibility and biological inertia. It has no sensitization. Genotoxicity test results show that PEEK does not cause any chromosome aberration. It can maintain stable physical and chemical properties under the stimulation of various chemical and physical conditions. It is an ideal material for prosthesis fabrication[4-6], thus, it is more suitable for preparing human bone tissue scaffolds and joint prostheses. A hotspot issue in the recent years has been how to fabricate the implants with a precise anatomical structure by combining 3D printing technology, and some clinical cases of PEEK prosthesis implantation have been reported[7]. However, none of these has involved the application of 3D-printed injection-molded PEEK lunate prosthesis in the treatment of stage III Kienböck’s disease.

Based on the anatomical and biomechanical characteristics of the wrist and combining the physical and chemical properties of PEEK materials, we prepared a PEEK lunate prosthesis by 3D printing and injection molding to substitute the necrotic lunate bone. This is the first case report of a 3D-printed injection-molded PEEK lunate prosthesis in the treatment of stage III Kienböck’s disease, and aimed to present a new therapy and the clinical outcome of the disease.

CASE PRESENTATION

Chief complaints
A 42-yr-old female patient was admitted to hospital for left wrist pain with movement limitation for 5 mo.

History of present illness
Before surgery, her symptoms lasted 5 mo. The pain was persistent, became aggravated during loading, and was relieved after rest. The pain was associated with limited mobility of the wrist joint.

History of past illness
The patient had no previous medical history.
Personal and family history
There is no history of genetic diseases and infectious diseases in the family.

Physical examination
The left wrist was slightly swollen, with obvious tenderness at the palmarar lunate, limited range of motion of wrist joint, decreased grip strength (Table 1), and normal peripheral blood flow and skin sensation.

Laboratory examinations
The patient's preoperative laboratory examination was unremarkable.

Imaging examinations
X-ray, computed tomography (CT), and magnetic resonance imaging were performed, and the imaging findings suggested lunate necrosis of the left wrist joint (Figure 1).

FINAL DIAGNOSIS
The patient was diagnosed with stage III Kienböck’s disease according to the Lichtman staging.

TREATMENT
Preparation of lunate prosthesis
The precise 3D raw data of healthy lunate bone were acquired from the patient by CT examination, and then a 3D lunate model was constructed with reverse engineering methodology. Thereafter, a cutting plane of a 3D lunate model was created according to the individualized anatomical characteristics of lunate bone, and used to cut the 3D lunate model and obtain a 3D model of lunate prosthesis using a mirroring technique. Based on the 3D model of lunate prosthesis, a PEEK lunate prosthesis mold was prepared for injection molding by 3D printing. The mold, a high-strength prosthetic structure and a PEEK lunate prosthesis with a high surface smoothness (after good finishing with specific technology), a complete overall shape and dense material texture were fabricated by injection molding (Figure 2).

Surgical procedures
A longitudinal incision was made on the dorsal wrist, and the skin, subcutaneous tissue and dorsal extensor retinaculum were dissected layer by layer to expose the articular capsule of the lunate bone, and the perilunate ligaments were cut off to expose and completely remove the necrotic lunate bone (Figure 3A). Subsequently, the 3D-printed PEEK lunate prosthesis was inserted into the original anatomical position of the lunate bone (Figure 3B and C). After dorsal extension and palmar flexion reached a normal level through the repeated radioulnar deviation of the wrist and no prosthesis extrusion was observed, the lunate prosthesis was found with good matching by C-arm X-ray examination. The dorsal articular capsule and dorsal extensor retinaculum of the wrist were sutured layer by layer. After surgery, the wrist was fixed in the functional position using plaster slab for 4 wk.

OUTCOME AND FOLLOW-UP
One year after surgery at the last visit, the range of motion and grasp force of the affected wrist were nearly normal, but VAS score and Cooney score were both improved in both resting and loading states (Tables 1 and 2). The carpal height ratio and radial scaphoid angle were nearly normal, the imaging examination confirmed that the PEEK lunate prosthesis had good anatomical suitability and no rupture, extrusion and detachment to other carpal bones (Figure 4).

DISCUSSION
There are many therapies for Kienböck’s disease that have an uniform goal of conserving normal structure, restoring movement function, and relieving the clinical wrist symptoms[8]. Four surgical procedures are usually applied: Revascularization, biomechanical therapy, lunate resection, and substitute implantation[3]. Lunate resection often induces downward shift and disordered arrangement of the carpal bone, as well as causing wrist pain and dysfunction. Therefore, choosing a suitable substitute is important for reconstructing radiocarpal joint and restoring wrist function[9], thus lunate
Table 1 Comparison of wrist range of motion and grasp force

<table>
<thead>
<tr>
<th></th>
<th>Affected wrist</th>
<th>Healthy wrist</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Before operation</td>
<td>At last visit</td>
</tr>
<tr>
<td>Dorsal extension (°)</td>
<td>0-25/32</td>
<td>0-50/55</td>
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<tr>
<td>Palmar flexion (°)</td>
<td>0-20/28</td>
<td>0-45/52</td>
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<tr>
<td>Ulnar deviation (°)</td>
<td>0-10/15</td>
<td>0-25/33</td>
</tr>
<tr>
<td>Radical deviation (°)</td>
<td>0-5/9</td>
<td>0-15/17</td>
</tr>
<tr>
<td>GF (kg)</td>
<td>15-20</td>
<td>30/38</td>
</tr>
</tbody>
</table>

Comparison between before operation and at the last visit or between the affected wrist and the healthy wrist.

Table 2 Comparison of wrist VAS score and Cooney score

<table>
<thead>
<tr>
<th></th>
<th>VAS score</th>
<th>Cooney score</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Resting state</td>
<td>Loading state</td>
</tr>
<tr>
<td>Before operation</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>At last visit</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Comparison between before operation and at the last visit. FED VAS: Visual analog scale.

Figure 1 Preoperative imaging findings. A-C: Preoperative radiographs (A), computed tomography (B) and magnetic resonance imaging (C), the arrow shows the necrotic lunate bone.

resection + substitute implantation is a good therapy for Kienböck’s disease. Many substitutes are available to be implanted after lunate resection, for example, tendon mass, capital bone shift, metal ball, pisiform bone shift, titanium alloy prosthesis, silicone prosthesis, and bone cement implant[10]. Tendon mass and arcuated transparent cartilage are soft in the texture, and have poor long-term efficacy as wrist instability will easily happen after their implantation[11]. Mariconda et al[12] reported that tendon flap could be used for sufficient interposition in the cavity. After surgery, however, the low-strength tendon is incapable to transmit the stress, and wrist synovitis and radial–scaphoid joint changes easily occur.

The substitute implantation of capital and pisiform bone shift has complicated surgery and can damage the structure and partial function of the wrist. The hard metal ball causes abrasion against the adjacent carpal bones; the titanium alloy prosthesis is expensive and requires premature customization, and it is difficult to adjust the size of such prosthesis and achieve the simulation[13]; and the bone cement prosthesis presents an unavoidable friction against the adjacent bones, which may lead to the abrasion and injury of the articular facet. Viljakka et al[14] reported that the silicone prosthesis had high hardness but poor tissue compatibility; thus, prosthesis extrusion and silicone synovitis can happen after implantation, followed by prosthesis damage and abrasion, further aggravating injury of adjacent joints. Therefore, the silicone prosthesis cannot meet the long-term functional demand of patients. The above-mentioned surgical procedures all have some limitations and vary in their clinical efficacy.
Söhling et al\[15\] reported that implants made of biomaterials have become an integral part of modern medicine. Therefore, the ideal implant is reactive, but does not cause foreign body reaction. Elucidating the early immune response in the foreign body reaction is implant-material specific. Tanca et al\[16\] also reported application of 2D-fluorescence difference gel electrophoresis (2D-DIGE) to formalin-fixed diseased tissue samples from hospital repositories, and showed that 2D-DIGE can support biomarker discovery and validation studies on large sample cohorts. The associated patient information can considerably boost studies with limited sample availability or those involving long-distance exchange of samples. Kyriakides et al\[17\] reported the foreign body reaction to synthetic polymer biomaterials and the role of adaptive immunity, and suggested the existence of crosstalk between innate and adaptive immune cells that depends on the nature of the implants.
PEEK is a high-performance polymer that has been used for the manufacturing of dental implants. PEEK is a material with high biocompatibility, good mechanical properties, high temperature resistance, chemical stability, polishability, good wear resistance, low plaque affinity and high bond strength with veneering composites and luting cements. Compared to rigid framework materials such as zirconium oxide and metal alloys, PEEK has a low modulus of elasticity of 4 GPa and is as elastic as bone, providing a cushioning effect and reduction of stresses transferred\[4,5\]. Thus, PEEK is more suitable for fabricating human bone tissue scaffolds and artificial joints. With such advantages as a short processing cycle, less material consumption and complex shaping, 3D printing technology better meets the clinical demand of individualized prosthesis customization. In addition, the prostheses may be fabricated with varying rigidity and elasticity by temperature control during 3D printing\[4\]; thus, a prosthesis can be designed which has a shape and size normally coincident to the original lunate bone and complies with the physiological characteristics of wrist. As a result, 3D-printed PEEK lunate prosthesis is a good choice. As the lunate bone has an irregular shape, the preoperative prosthesis design is important and focuses on the width, height and concave of lunate bone to keep the original size as much as possible. A prosthesis that is too big bears excessive pressure and thus become ruptured and extruded, while one that is too small size cannot stabilize the joint.

PEEK has outstanding tribological properties, excellent sliding and fretting wear resistance, especially high wear resistance and low friction coefficient at 250°C. It is easy for extrusion and injection molding, with excellent processing performance and high molding efficiency. As a medical implant, its elastic modulus is similar to that of bone, with good biocompatibility and transparent rays. The material is resistant to simulated in vivo degradation, including damage caused by lipid exposure. Although PEEK has these excellent characteristics\[4\], it still has some problems as a bone implant. One of them is that there is still a gap between PEEK and human bone in terms of modulus and mechanical strength. In terms of mechanical strength, PEEK still cannot meet the needs of human bones. Another problem with PEEK as a medical implant is that it is biologically inert\[5\]. Its low reactivity and integration with surrounding tissues will affect the successful transplantation of PEEK in vivo. In the next step of the treatment of lunar osteonecrosis, we plan to modify PEEK to better increase its mechanical strength and better match its elastic modulus.

CONCLUSION

In summary, the 3D-printed injection-molded PEEK lunate prosthesis demonstrates definite efficacy in treating stage III Kienböck’s disease, and it is an effective therapy worthy of being popularized. Although such prosthesis has good clinical efficacy, the subsequent large-sized long-term clinical case observation is needed.

FOOTNOTES

Author contributions: Yuan CS and Tang KL contributed equally to this work; Yuan CS, Tang Y, Xie HQ, Liang TT and Tang KL designed the research study; Operative procedures were carried out by Tang KL; Yuan CS and Tang Y completed manuscript writing; Date collection and results evaluation were completed by Xie HQ and Liang; all authors have read and approve the final manuscript.

Supported by Chongqing Science and Health Combined Medical Discipline, No. 2020MSXM012.
Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors report no relevant conflict of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wu YXJ
L-Editor: A
P-Editor: Wu YXJ

REFERENCES


High scored thyroid storm after stomach cancer perforation: A case report

Seung Min Baik, Yejune Pae, Jae-Myeong Lee

BACKGROUND
Thyroid storm is a life-threatening emergency. Reportedly, the prevalence of thyroid storm is 1%-2% among patients admitted to the hospital for thyrotoxicosis. Burch and Wartofsky (1993) introduced a scoring system using precise clinical criteria to identify thyroid storms. Only 17 cases of thyroid storm with a score > 70 points have been reported. Although thyroid storms are uncommon, their clinical findings resemble those of sepsis.

CASE SUMMARY
A 48-year-old man was referred to the emergency room from a local clinic owing to suspicion of gastric ulcer perforation; medications for hypertension, diabetes mellitus, and hyperthyroidism had been suspended 1 year prior to this visit. We performed an emergency distal gastrectomy with Billroth II anastomosis for gastric cardia cancer perforation, and the patient was referred to the surgical intensive care unit (ICU). On the 2nd d in the ICU, his body temperature (BT) increased to 41.3 °C at 19:00, with the thyroid storm score (90 points) peaking at 18:00 (BT; 41.2°C, pulse rate; 138/min, irritable status). The patient was administered propylthiouracil, intravenous glucocorticoids, acetaminophen, and Lugol’s solution daily. Subsequently, we performed bladder irrigation with cold saline using a Foley catheter and applied a hypothermic blanket to decrease the patient's BT. His vital signs were stable on the 8th day in the ICU.

CONCLUSION
Thyroid storms are uncommon, with few reports in the literature; however, their clinical findings resemble those of sepsis and require further investigation. Since
an untreated thyroid storm results in a high mortality rate, it should be investigated when managing sepsis.

**Key Words:** Thyroid storm; Stomach cancer; Severity score; Sepsis; Case report

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**Core Tip:** Since thyroid storm is a life-threatening emergency and mortality is high when treatment is delayed, thyroid function evaluation should not be overlooked when managing sepsis.

**INTRODUCTION**

Thyroid storm is a life-threatening emergency. Reportedly, the prevalence of thyroid storm 1%-2% among patients admitted to the hospital for thyrotoxicosis[1]. In a nationwide survey of hospitals in Japan, the incidence of thyroid storm in hospitalized patients was 0.22% among all patients with thyrotoxicosis and 5.4% of patients admitted to the hospital for thyrotoxicosis[2,3]. Thyroid storm can develop in patients with long-standing untreated hyperthyroidism and can be precipitated by an acute event such as thyroid or non-thyroidal surgery, trauma, infection, an acute iodine load, or parturition[4].

Recent data suggest that the mortality rate of thyroid storms is approximately 10%-30%[1,2]. Multiple organ failure is the most common cause of death, followed by congestive heart failure, respiratory failure, arrhythmia, disseminated intravascular coagulation, gastrointestinal perforation, hypoxic brain syndrome, and sepsis[2,3].

Thyroid storm is diagnosed by clinical findings. Burch and Wartofsky (1993) introduced a scoring system using precise clinical criteria for the identification of thyroid storms[5]. Based on these criteria, a score of < 25 points indicates that a thyroid storm is unlikely; 25-44 points an impending thyroid storm; and ≥ 45 points, thyroid storm. There is no concept of a “severe” thyroid storm. However, to the best of our knowledge, only 17 cases of thyroid storm with a score > 70 points have been reported. Among these 17 cases, only four cases had a score of 90 points. Although thyroid storms are uncommon, their clinical findings resemble those of sepsis.

Here, we report a case of thyroid storm with a score of 90 points after gastric perforation surgery, and we analyze the “severe” form of thyroid storm (with a score > 70 points) in the 17 cases reported in the literature.

**CASE PRESENTATION**

**Chief complaints**

In the emergency room (ER), he complained of nausea, diffuse abdominal pain, general weakness, anorexia, and indigestion, which had started 4 d prior to admission.

**History of present illness**

A 48-year-old male patient was referred to the ER from a local clinic owing to suspicion of gastric ulcer perforation. We performed an emergent distal gastrectomy with Billroth II anastomosis for gastric cardia cancer perforation, a palliative surgery performed owing to peritoneal tumor seeding. The total operating time was 3 h and 55 min, and the patient's vital signs were stable during surgery. Postoperatively, the patient was referred to the surgical intensive care unit (ICU), and his vital signs were checked every hour.

**History of past illness**

He had a medical history of hypertension, type II diabetes mellitus (DM), and hyperthyroidism. One year ago, he had stopped taking medications for hypertension, DM, and hyperthyroidism.
Personal and family history
The patient’s personal and family history information could not be obtained.

Physical examination
On physical examination, he presented with hypoactive bowel sounds and direct tenderness in the epigastric area.

Laboratory examinations
Laboratory examination in the ER showed the following results: white blood cell counts $12.5 \times 10^3/\mu L$, erythrocyte sedimentation rate 38 mm/h, and C-reactive protein 16.93 mg/dL.

The results of thyroid function tests are shown in Table 1. The free T4, T3, and T4 Levels exceeded the normal range, while thyroid stimulating hormone levels were below the normal range. The other laboratory results were non-specific.

Imaging examinations
Computed tomography in the ER revealed peritonitis due to gastric ulcer perforation and gastric malignancy with suspected peritoneal carcinomatosis.

FINAL DIAGNOSIS
On the 2nd day in the ICU, the patient’s body temperature (BT) increased to 41.3 °C at 19:00, and the thyroid storm score peaked at 18:00 (BT 41.2 °C; pulse rate: 138/min); furthermore, he was irritable; had a Glasgow Coma Scale score of E3V1M5, with eye opening to speech, no verbal response, and localized motor response to pain; and complained of severe pain (Table 2). The patient’s highest score for a thyroid storm was 90.

TREATMENT
The patient was administered a daily dose of oral propylthiouracil (PTU) 800 mg, PTU enema 400 mg, intravenous glucocorticoids 40 mg, oral acetylsalicylic acid 650 mg, and oral Lugol’s solution 1.5 mL. Subsequently, we performed bladder irrigation with cold saline using a Foley catheter and applied a hypothermic blanket to decrease the patient’s BT.

On the 3rd day in the ICU, the PTU dose was increased to 1200 mg/d, while the doses of the other drugs were maintained. From the 4th day, the oral PTU dose was fixed at 200 mg, q6hd; Lugol’s solution (0.5 mL; q8hd) was also delivered. On the 9th day, the patient was referred to the general ward, with the administration of oral PTU 200 mg four times daily and tapering of glucocorticoid therapy.

OUTCOME AND FOLLOW-UP
The patient’s vital signs were stable from the 8th postoperative day, and he showed clear mental status on the 4th postoperative day (Figure 1). In the general ward, on the 15th day, the oral PTU dose was decreased to 200 mg three times daily. On the 29th hospital day, he was discharged with an asymptomatic status, stable vital signs, and a prescribed dose of oral PTU 200 mg three times daily.

DISCUSSION
We report a case of thyroid storm with extremely high fever (41.3 °C), typically associated with patient mortality. Indeed, high fever alone increases mortality in ICU patients[6].

While this patient’s BT was < 40 °C in the ER, it increased to > 40°C postoperatively. Later, the patient presented with tachycardia (peaked at 138/min), irritability, and abdominal pain; he also had a history of hyperthyroidism, with a high score of 90 points in the thyroid storm scoring system, which reflects disease severity. Based on the scoring system, thyroid storms are considered unlikely for scores of < 25 points, while 25-45 points suggest impending storms; a score of > 45 points is highly associated with thyroid storms[5] (Table 2). Therefore, when the score approaches 45 points, the patient needs more intensive monitoring and re-evaluation for thyroid storm. The mortality risk associated with thyroid storm is estimated to be 8%-25%, despite modern advancements in treatment and supportive measures[7].
Table 1 Thyroid function test values of the patient

<table>
<thead>
<tr>
<th>Hormone (normal range, unit)</th>
<th>At ER (preoperation)</th>
<th>Postop. day 6</th>
<th>Postop. day 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3 (60.0-181.0, ng/dL)</td>
<td>625.4</td>
<td>79.9</td>
<td>94.1</td>
</tr>
<tr>
<td>T4 (4.50-10.90, ng/dL)</td>
<td>27.27</td>
<td>5.80</td>
<td>12.45</td>
</tr>
<tr>
<td>fT4 (0.89-1.76, ng/dL)</td>
<td>7.02</td>
<td>1.90</td>
<td>3.58</td>
</tr>
<tr>
<td>TSH (0.55-4.78, uIU/mL)</td>
<td>&lt; 0.008</td>
<td>&lt; 0.008</td>
<td>&lt; 0.008</td>
</tr>
</tbody>
</table>

ER: Emergency room; Postop.: Postoperative; TSH: Thyroid stimulating hormone.

Table 2 Summary severity scores of previously reported thyroid storm cases over 70 points and the present case

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Gender</th>
<th>BT</th>
<th>CNS effect</th>
<th>Gl-hepatic dysfx.</th>
<th>CV dysfx.</th>
<th>HF</th>
<th>Pre. Hx.</th>
<th>Total</th>
<th>Mortality</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40/Male</td>
<td>20</td>
<td>30</td>
<td>20</td>
<td>35</td>
<td>10</td>
<td>0</td>
<td>115</td>
<td>No</td>
<td>Shimoda et al[8], 2014</td>
</tr>
<tr>
<td>2</td>
<td>50/Female</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>35</td>
<td>5</td>
<td>10</td>
<td>90</td>
<td>No</td>
<td>Izumi et al[9], 2009</td>
</tr>
<tr>
<td>3</td>
<td>48/Male</td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>25</td>
<td>10</td>
<td>10</td>
<td>85</td>
<td>No</td>
<td>Sasaki et al[10], 2011</td>
</tr>
<tr>
<td>4</td>
<td>30/Female</td>
<td>15</td>
<td>30</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>10</td>
<td>80</td>
<td>Yes</td>
<td>Yamaji et al[11], 1991</td>
</tr>
<tr>
<td>5</td>
<td>43/Male</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>25</td>
<td>5</td>
<td>10</td>
<td>80</td>
<td>No</td>
<td>Diaz et al[12], 2009</td>
</tr>
<tr>
<td>6</td>
<td>62/Female</td>
<td>20</td>
<td>0</td>
<td>10</td>
<td>25</td>
<td>15</td>
<td>0</td>
<td>70</td>
<td>No</td>
<td>Jha et al[13], 2012</td>
</tr>
<tr>
<td>7</td>
<td>55/Female</td>
<td>0</td>
<td>20</td>
<td>10</td>
<td>25</td>
<td>5</td>
<td>10</td>
<td>70</td>
<td>No</td>
<td>Ogiso et al[14], 2008</td>
</tr>
<tr>
<td>8</td>
<td>56/Female</td>
<td>0</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>70</td>
<td>No</td>
<td>Yoshino et al[15], 2010</td>
</tr>
<tr>
<td>9</td>
<td>50/Male</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>25</td>
<td>0</td>
<td>10</td>
<td>70</td>
<td>Yes</td>
<td>Hosojima et al[16], 1992</td>
</tr>
<tr>
<td>10</td>
<td>51/Female</td>
<td>15</td>
<td>10</td>
<td>0</td>
<td>25</td>
<td>15</td>
<td>10</td>
<td>75</td>
<td>No</td>
<td>Nai et al[17], 2018</td>
</tr>
<tr>
<td>11</td>
<td>52/Male</td>
<td>5</td>
<td>20</td>
<td>10</td>
<td>30</td>
<td>10</td>
<td>0</td>
<td>75</td>
<td>No</td>
<td>Andrade et al[18], 2018</td>
</tr>
<tr>
<td>12</td>
<td>36/Female</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>20</td>
<td>15</td>
<td>10</td>
<td>75</td>
<td>No</td>
<td>Sugiyama et al[19], 2017</td>
</tr>
<tr>
<td>13</td>
<td>24/Female</td>
<td>30</td>
<td>10</td>
<td>10</td>
<td>25</td>
<td>0</td>
<td>10</td>
<td>85</td>
<td>No</td>
<td>McMillen et al[20], 2016</td>
</tr>
<tr>
<td>14</td>
<td>65/Male</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>35</td>
<td>5</td>
<td>0</td>
<td>70</td>
<td>No</td>
<td>Snyder et al[21], 2020</td>
</tr>
<tr>
<td>15</td>
<td>59/Female</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>25</td>
<td>0</td>
<td>10</td>
<td>75</td>
<td>No</td>
<td>Osada et al[22], 2011</td>
</tr>
<tr>
<td>16</td>
<td>50/Female</td>
<td>15</td>
<td>20</td>
<td>10</td>
<td>35</td>
<td>10</td>
<td>0</td>
<td>90</td>
<td>No</td>
<td>Umezu et al[23], 2013</td>
</tr>
<tr>
<td>17</td>
<td>41/Female</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>35</td>
<td>15</td>
<td>10</td>
<td>90</td>
<td>No</td>
<td>Kulaksizoglu et al[24], 2012</td>
</tr>
<tr>
<td>18</td>
<td>48/Male</td>
<td>30</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>0</td>
<td>10</td>
<td>90</td>
<td>No</td>
<td>Present case</td>
</tr>
</tbody>
</table>

BT: Body temperature; CNS: Central nervous system; Gl-hepatic dysfx.: Gastrointestinal-hepatic dysfunction; CV: Cardiovascular; HF: Heart failure; Pre.Hx.: Precipitant history.

In this case, the extremely high BT (41.3 °C), elevated pulse rate (PR) (138/min), and altered Glasgow Coma Scale score (E3V1M5) observed on the 2nd day in the ICU were immediately considered to indicate thyroid storm, and treatment was initiated. Severity was assessed at the same time as the diagnosis using the scoring system. The patient was diagnosed with gastric ulcer perforation. Therefore, these symptoms may be considered as signs of sepsis.

To the best of our knowledge, there are some reports of cases with scores of < 70 points; however, there are only 17 reported cases with scores of ≥ 70 points [8-24] (Table 2). Among the 17 cases with scores of ≥ 70 points, two involved mortality. Case 1 involved the highest severity score, with 115 points. In case 1, the patient had no previous medical or family history of thyroid disease (0 points). Laboratory findings showed liver dysfunction with jaundice (20 points), while physical examination revealed the following: atrial flutter with a PR of 162/min (35 points), high fever (39.3 °C) (20 points), impaired consciousness (30 points), and reduced ejection fraction (43%) with moderate bilateral pleural effusion (10 points). The patient in case 1 was discharged from the hospital on day 94. In the two mortality cases, the severity scores were 80 and 70. In the mortality case with a severity score of 80 points, the central nervous system dysfunction score was very high (30 points). Meanwhile, in the mortality case with a
severity score of 70 points, the cardiovascular dysfunction score was 25 points, which was relatively high compared to other scores. However, the total severity scores in the mortality cases were not relatively high compared to those of other thyroid storm cases. In all 18 cases, including our case, no correlation was found between the severity score and mortality; nevertheless, the number of cases is insufficient to draw a valid conclusion.

Comparing our case to the other 17 cases reported in the literature, we found that our patient presented with extremely high fever and a high severity score. In cases with the same score (cases 2, 16, 17, and 18 [present case]), the highest-scored factor differed between cases. Meanwhile, cases 2, 16, and 17 had high scores for cardiovascular dysfunction (PR > 140/min with atrial fibrillation), and the present case involved a high BT (41.3 °C).

High fever and tachycardia are the main parameters of systemic inflammatory response syndrome, as per the criteria established in 1991[25]. In the Sepsis-3 criteria, newly established in 2016, PR and BT were not included[26]. Although PR and BT were excluded from the diagnostic criteria for sepsis, they are still important in managing sepsis. On the other hand, thyroid storm is not a major consideration in ICU. Therefore, when uncontrolled fever or tachycardia is observed, it may be useful for the physician to consider evaluation of thyroid function. The reason is that sepsis-induced tachycardia and high fever are improved by appropriate sepsis management, but the signs induced by thyroid storm are different in treatment guidelines such as antithyroid agents, Lugol’s solution and steroid etc.

CONCLUSION

In general, thyroid function tests are not performed before emergency surgery for bowel perforation. Tachycardia and high fever are commonly observed postoperatively. However, since thyroid storm is a life-threatening emergency and mortality is high when treatment is delayed, thyroid function evaluation should not be overlooked when managing sepsis.

FOOTNOTES

Author contributions: Lee JM and Baik SM designed the research study; Lee JM, Baik SM and Pae Y performed the research, analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

Informed consent statement: The study was approved by the Institutional Review Board (IRB) (approval number: 2021AN0281) and waived the informed consents due to the retrospective study.
Conflict-of-interest statement: All authors declare that they have no conflicts of interest related to this work.

CARE Checklist (2016) statement: All authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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REFERENCES

Baik SM et al. High scored thyroid storm after stomach cancer perforation

18 Andrade Luz I, Pereira T, Catorze N. Thyroid storm: a case of haemodynamic failure promptly reversed by aggressive medical therapy with antithyroid agents and steroid pulse. BMJ Case Rep 2018; 11 [PMID: 30567262 DOI: 10.1136/bcr-2018-226669]


20 McMillen B, Dhillon MS, Yong-Yow S. A rare case of thyroid storm. BMJ Case Rep 2016; 2016: 10.1136/bcr-2016


Cholecystitis—an uncommon complication following thoracic duct embolization for chylothorax: A case report

Le Viet Dung, Ma Mai Hien, Thieu-Thi Tra My, Doan Tien Luu, Le Tuan Linh, Nguyen Minh Duc

Abstract

BACKGROUND
Chylothorax is an uncommon condition in which chyle leaks into the pleural cavity, and biliary peritonitis is a rare complication of thoracic duct embolization in clinical practice.

CASE SUMMARY
We describe the case of a 50-year-old woman who presented with chylothorax and underwent thoracic duct embolization using a coil and a mixture of histoacryl glue and lipiodol. The patient developed upper abdominal pain and fever after the intervention. She was diagnosed with biliary peritonitis and treated with cholecystectomy at Hanoi Medical University Hospital.

CONCLUSION
Although thoracic duct embolization is considered a safe and minimally invasive procedure, it is not without risk. Following thoracic duct embolization, severe or persistent abdominal pain should be explored utilizing imaging data and laboratory results to determine problems as soon as possible.

Key Words: Lymphangiography; Thoracic duct embolization; Cholecystitis; Chyle leakage; Biliary peritonitis; Case report

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Core Tip: Chyl thorax is a condition in which chyle leaks into the pleural cavity. Trauma, spontaneous (non-traumatic), and idiopathic etiologies are all potential causes of chyl thorax. In clinical practice, biliary peritonitis is an uncommon consequence of thoracic duct embolization. Despite its reputation as a safe and minimally intrusive technique, thoracic duct embolization is not without hazard. Severe or chronic abdominal discomfort should be investigated as soon as possible after thoracic duct embolization, using imaging data and laboratory results to identify issues.

Citation: Dung LV, Hien MM, Tra My TT, Luu DT, Linh LT, Duc NM. Cholecystitis-an uncommon complication following thoracic duct embolization for chyl thorax: A case report. World J Clin Cases 2022; 10(24): 8775-8781
URL: https://www.wjgnet.com/2307-8960/full/v10/i24/8775.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i24.8775

INTRODUCTION
Chyl thorax is a rare disease characterized by chyle leakage into the pleural cavity. The etiology of chyl thorax can be traumatic, idiopathic, and non-traumatic including malignancies, primary lymphatic disorders or congenital malformations[1]. Conservative management consisting of dietary control and drainage is typically the first-line treatment. Interventional radiology and surgery are considered if conservative management fails[1]. Thoracic duct embolization is a new, safe, and effective method for chyl thorax treatment, it is associated with minimal complications[2,3], and these attributes have contributed to the recent increase in the use of thoracic duct embolization as a first-line treatment for chyl thorax[4]. In this case report, we describe the occurrence of biliary peritonitis following thoracic duct embolization for the treatment of chyl thorax due to penetration of a percutaneous interventional needle into the gallbladder wall.

CASE PRESENTATION

Chief complaints
A 50-year-old woman presented at Hanoi Medical University Hospital with dyspnea and chest pain.

History of present illness
The symptoms started 1 mo prior to presentation, with chest discomfort.

History of past illness
Medical records were normal.

Personal and family history
There was no personal and family history of other diseases.

Physical examination
Physical examination was not special. On auscultation, vesicular breath sound was diminished with decreased vocal resonance especially at the middle and lower lobes of the right lung.

Laboratory examinations
Blood tests at presentation were in the normal range. Her pleural fluid analysis showed: Triglyceride 20.3 mmol/L and cholesterol 2.2 nmol/L.

Imaging examinations
Contrast-enhanced magnetic resonance (MR) lymphangiography was performed to obtain coronal and axial T1-weighted and T1-weighted fat-saturated post-gadolinium images, which showed a large right pleural effusion and contrast agent leakage from the right-sided branch of the lower-third of the thoracic duct into the right pleural space (Figure 1) and a double thoracic duct variant.
INITIAL DIAGNOSIS

Further diagnostic work-up
A multidisciplinary consultation (involving respirologists, interventional radiologists, nutritionist) was performed. Three days after presentation, the patient underwent an intranodal lymphangiogram using digital subtraction angiography (DSA), which revealed dilated lymphatic vessels and lymphatic malformations in the lower-third of the thoracic duct, resulting in the leakage of contrast agent into the right pleural space (Figure 2). The patient also had a double lower thoracic duct variant. As the leakage was clear on MR lymphangiography and the patient had a large right pleural effusion (Figure 1), we decided to treat her with lymphatic embolization, combined with lipiodol fasting. Under DSA guidance, the cisterna chyli was accessed percutaneously through the anterior abdominal wall with a 22-gauge Chiba needle. A right transabdominal approach was performed to avoid the aorta. The contrast was injected to confirm appropriate placement in the cisterna chyli. A wire was then advanced through the needle and placed within the thoracic duct. The thoracic duct below the leak was embolized under DSA, using a coil and a mixture of histoacryl glue and lipiodol.

Several hours after this intervention, the patient reported moderate–severe epigastric and right quadrant pain. Contrast-enhanced computed tomography (CT) was immediately performed, which showed wall thickening and subserosal edema in the gallbladder (Figure 3), with peripancreatic fluid extending into the pararenal spaces and bilateral paracolic gutters. The pancreas was homogeneously enhanced, with no signs of necrosis or pancreatic duct dilatation. A small, high-density nodule was observed in the gallbladder wall. The initial diagnosis was acute pancreatitis after lymphatic intervention; thus, she underwent conservative treatment instead of surgery. The respiratory symptoms were resolved by the intervention, but the patient experienced increasing abdominal pain and mild fever. Blood tests revealed an infectious condition: white blood cell count (WBC), 13.5 G/L; neutrophils, 88.7%; and C-reactive protein (CRP), 3.49 mg/dL. Pancreatic enzymes were within the normal range: amylase, 84 U/L; lipase, 20 U/L; and total/direct bilirubin, 9.6/5.7 µmol/L. A second contrast-enhanced abdominal CT performed 3 days later revealed further gallbladder wall thickening (approximately 20 mm) and subserosal edema (Figure 4), with no signs of stones, pseudoaneurysm, or contrast agent leakage. The small, high-density nodule on the gallbladder wall and approximately 30 mm of ascites were observed.

FINAL DIAGNOSIS
The final diagnosis was biliary peritonitis following thoracic duct embolization for chylothorax treatment. The critical finding was the high-density nodule observed on the gallbladder wall, which corresponded to lipiodol deposition following penetration of the percutaneous interventional needle into the gallbladder wall.

TREATMENT
The patient underwent emergency laparoscopic cholecystectomy. The surgeon described 300 mL of bile fluid in the abdominal cavity. The gallbladder was inflamed and covered with greater omentum. The surgeon diagnosed biliary peritonitis in this case. Two holes (approximately 1 mm) were identified in
Figure 2 Intranodal lymphangiogram using digital subtraction angiography prior to treatment. Frontal image of digital subtraction angiography revealed dilated lymphatic vessels and a lymphatic malformation in the lower thoracic duct (orange arrow), resulting in the leakage of contrast agent into the right pleural space.

Figure 3 Contrast-enhanced computed tomography after intervention. Axial image showed gallbladder wall thickening of approximately 14 mm and subserosal edema (blue arrow). Peripancreatic fluid is observed extending into the pararenal spaces (white arrow) and bilateral paracolic gutters. A small, high-density nodule is observed in the gallbladder wall (orange arrow).

the base and funnel of the gallbladder (Figure 5), suggesting penetration of the gallbladder wall by the percutaneous interventional needle.

OUTCOME AND FOLLOW-UP

After surgery, the patient improved clinically, and the chylothorax output gradually resolved after several weeks. Inflammatory markers remained slightly elevated, and bilirubin returned to the normal range within 5 days: WBC, 9.3 G/L; neutrophils, 82%; CRP, 2.84 mg/dL; and total/direct bilirubin, 3.2/12.2 µmol/L. Abdominal ultrasound showed mild fat stranding around the gallbladder bed and 24 mm of right pleural effusion. The patient was discharged from the hospital 5 days after surgery.
**Figure 4** Contrast-enhanced abdominal computed tomography after 3 days. Axial image shows further increased gallbladder wall thickening (~20 mm) and subserosal edema (blue arrow), without evidence of stones, pseudoaneurysm, or contrast agent leakage. A small, high-density nodule can be observed in the gallbladder wall (white arrow).

**Figure 5** Laparoscopic cholecystectomy. Image revealed 2 holes 1 mm in size (black arrows) in the base and funnel of the gallbladder.

**DISCUSSION**

Lymphatic intervention was first described by Cope *et al* [5], and advances in interventional techniques continue to be developed. The efficacy of lymphatic intervention has been reported by many authors [2, 6, 7]. Thoracic duct embolization is a new and minimally invasive approach with a high success rate and low morbidity and mortality rates [2]. Cope and Kaiser reported a response rate of 73.8% after thoracic duct embolization with no morbidity or mortality [4]. The overall clinical success rate reported by Pamarthi *et al* [3] was 72%, and Itkin *et al* [7] reported a success rate of 90%.

According to the Society of Interventional Radiology Clinical Practice Guidelines, post-intervention complications can be categorized as major or minor complications [8]. Major complications of lymphatic interventions include pulmonary or portal vein embolism caused by glue or guidewire fragment retention. Minor complications often include anesthesia side effects, skin injuries, or perihepatic hematoma [3]. In addition, some delayed mild complications as observed by Laslett *et al* [9] are lower-extremity edema and chronic diarrhea.

Cope *et al* [4] reported no complications associated with thoracic duct embolization. Pamarthi *et al* [3] and Itkin *et al* [7] reported complication rates of 6.7% and 3%, respectively. Although limited data are available regarding complications, several articles have reported pulmonary embolisms associated with glue, chylous ascites, perihepatic hematoma, bile leakage, or bile peritonitis [3, 10, 11].

As chylothorax in this patient lasted for 1 mo, not an emergency condition, we decided to treat after a multidisciplinary consultation. Therefore, thoracic duct embolization was performed 3 days after hospitalization. Our patient experienced moderate-severe abdominal pain and fever following thoracic duct embolization, which increased over several days. A contrast-enhanced abdominal CT performed immediately after the intervention revealed that the gallbladder wall was thick and edematous, with peripancreatic fluid extending to the bilateral anterior pararenal space and paracolic gutters. The initial diagnosis was pancreatitis, which is also an extremely uncommon complication following thoracic duct embolization.
embolization\[12]. Unfortunately, the clinical presentation, laboratory tests, and imaging with contrast-enhanced abdominal CT 3 days later were not compatible with the initial diagnosis. We reviewed the initial CT images and realized that we missed a critical sign: a small, high-density nodule in the gallbladder wall, corresponding to lipiodol deposition due to penetration of the percutaneous interventional needle into the gallbladder wall. As the needle punctured through the right abdominal wall, it penetrated into the gallbladder. Although this is a rare complication infrequently reported in the literature, we suggest that the cisterna chyli should be accessed under DSA accompanied by ultrasound in order to avoid accidental puncture in the future. The patient had symptoms of peritonitis, and bile in the abdominal cavity was confirmed intraoperatively. Thus, the final diagnosis was biliary peritonitis. This case serves as a reminder for clinicians and radiologists of the importance of correct diagnosis following the initial CT scan to allow for timely cholecystectomy.

CONCLUSION

We report a rare case of cholecystitis following thoracic duct embolization to treat chylothorax due to penetration of the interventional needle into the gallbladder wall. Although thoracic duct embolization is considered to be a safe and minimally invasive method, several major complications may occur. Severe or persistent abdominal pain after intervention should be investigated using imaging findings and laboratory results to diagnose complications following thoracic duct embolization in a timely manner.

FOOTNOTES

Author contributions: Dung LV, Hien MM, Luu DT, and Linh LT prepared the case file retrieval and case summary; Dung LV, Hien MM, and Duc NM designed the research; Dung LV, Hien MM, and Tra My TT performed the research; Dung LV and Duc NM wrote the paper; all authors read and approved the final manuscript.

Informed consent statement: Our institution does not require ethical approval for reporting individual cases or case series. Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Ma YJ
L-Editor: Webster JR
P-Editor: Ma YJ

REFERENCES

Iatrogenic cholecystitis following thoracic duct embolization


Endometrial squamous cell carcinoma originating from the cervix: A case report

Xin-Yu Shu, Zhang Dai, Shuang Zhang, Hui-Xia Yang, Hui Bi

Specialty type: Obstetrics and gynecology
Provenance and peer review: Unsolicited article; Externally peer reviewed.
Peer-review model: Single blind
Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0
P-Reviewer: Mainenti PP, Italy; Šarenac TM, Serbia
Received: April 14, 2022
Peer-review started: April 14, 2022
First decision: May 31, 2022
Revised: June 12, 2022
Accepted: July 20, 2022
Article in press: July 20, 2022
Published online: August 26, 2022

Abstract

BACKGROUND
Cervical squamous cell carcinoma (SCC) is the most common type of cervical carcinoma and is generally derived from a precancerous stage called cervical high-grade squamous intraepithelial lesion (HSIL). Usually, the cancer metastasizes through lymphatic or hematogenous dissemination, but rarely spreads upward into the uterus. Here, we report a case of cervical HSIL extending into the endometrium and finally progressing to SCC in the uterine cavity.

CASE SUMMARY
A 57-year-old postmenopausal woman visited our department and requested a routine cervical check-up. Four years ago, she had undergone a cervical loop electrosurgical excision procedure because of HSIL found during the gynecological examination, and she had not been checked again since. This time, a relapse of the cervical HSIL was diagnosed along with uterine pyometra and endometrial polyps. After 2 wk of antibiotic treatment, a laparoscopic hysterectomy was performed, and the final pathological examination revealed that the cervical HSIL had spread directly upward into the uterine cavity, gradually developing into cervical SCC in the endometrium.

CONCLUSION
Cervical HSIL/SCC can directly spread upward into the uterus with the most common symptoms of pyometra and cervical stenosis. More attention should be given to the early detection and prevention of this disease.

Key Words: Endometrial squamous cell carcinoma; Superficial spreading; Cervical carcinoma; Pyometra; Cervical stenosis; Case report

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Core Tip: Under unique circumstances, cervical cancer or precancerous lesions can spread directly upward into the uterine cavity, forming endometrial squamous cell carcinoma, which may alter staging and affect prognosis. Emphasis should be placed on prevention as well as early diagnosis, and although a gynecological ultrasound and an endometrial biopsy may help, their impact is still limited. It is imperative to explore the best clinical strategies for treating this disease.

INTRODUCTION

Cervical cancer is the fourth most common cancer among women globally[1]. Among its various classifications, squamous cell carcinoma (SCC) is the most common type and is generally derived from a precancerous stage called cervical high-grade squamous intraepithelial lesion (HSIL). Normally, the tumor extends downward into the vagina or laterally, invading the parametric tissue, and it also metastasizes through the lymphatic glands or by blood dissemination. Rarely does it spread directly upward into the endometrium, forming endometrial SCC, which is called superficial spreading SCC[2]. Here, we report a case of a postmenopausal woman who underwent hysterectomy because of a relapse of cervical HSIL, whose pathology revealed that the cervical HSIL had transformed into endometrial SCC.

CASE PRESENTATION

Chief complaints
A 57-year-old postmenopausal woman came to our department requesting a routine cervical check-up.

History of present illness
Four years ago, the patient was positive for human papillomavirus (HPV) 16, and had a negative Thinprep cytologic test during pelvic examination. The patient did not have any abnormal vaginal bleeding or abdominal pain. A colposcopic examination showed cervical HSIL, and partial invasion could not be excluded. Soon after, she underwent a cervical loop electrosurgical excision procedure (LEEP), and the pathological examination later revealed cervical HSIL, with a positive endocervical margin (also HSIL). The patient refused a hysterectomy at that time and was lost to follow-up after a 3-mo colposcopic examination showed a normal postoperative appearance. This time, she denied having any symptoms and admitted that she had not had regular gynecological examinations during the past 4 years. The patient was still positive for HPV 16 with a negative cytology; however, a subsequent colposcopic examination revealed HSIL within her cervical canal.

History of past illness
The patient had a history of hypertension for > 30 years, diabetes for > 3 years, and had a cardiac stent implanted 3 years earlier; all these diseases were under good control.

Personal and family history
The patient had been menopausal for 3 years, gravida 1, para 1, and denied having a family history of malignant tumors.

Physical examination
Her pelvic examination was negative, and both her uterus and adnexa were atrophied.

Laboratory examinations
Her squamous cell carcinoma antigen was 1.8 ng/mL.

Imaging examinations
Gynecological ultrasound revealed a fluid-filled uterus and cervix measuring 71 mm × 32 mm × 29 mm, with an unevenly high echogenic mass adhering to the upper endometrium measuring 11 mm × 14 mm × 8 mm. Later, enhanced pelvic magnetic resonance imaging confirmed the findings, suggesting
pyometra and possibly endometrial polyps or submucosal myoma (Figure 1).

**FINAL DIAGNOSIS**

The patient was finally diagnosed with cervical HSIL, pyometra, and a suspected endometrial polyp.

**TREATMENT**

The patient was then scheduled for LEEP and hysteroscopic examination. During surgery, the cervix was stenotic, and after careful separation, a large amount of brown and odorless pus (approximately 30 mL) came out of the cervical canal. To prevent further infection, the surgery was postponed, and metronidazole hydrochloride was administered for 14 days. During this period, she did not suffer from fever or abdominal pain, and the pus culture was negative. Two weeks later, she underwent the planned surgery, and during hysteroscopy, we found that the endometrium was slightly thicker with two adherent polyp-shaped lumps. One of these was vascular hyperplasia, which we removed; subsequently, we performed curettage of the entire endometrium, along with a second LEEP. The pathology results showed chronic inflammation within the cervix, HSIL in the cervical canal, and endometrial polyps covered by HSIL. This time, after consultation, she decided to undergo a hysterectomy. The patient underwent laparoscopic hysterectomy and bilateral adnexectomy 3 mo later.

**OUTCOME AND FOLLOW-UP**

The surgery was successful; the patient recovered well postoperatively and was discharged 4 d after surgery. On macroscopic examination, the uterus was normal sized, weighed 50 g, with 5 mL pus inside (which was culture negative); the endometrium was thin, with a whitish and light brown appearance, and there was polypoid gray tissue extending to the right uterine cornua. Both ovaries were atrophic, along with the fallopian tubes, and the endometrium was unremarkable. Under microscopic examination, the cervix showed HSIL with chronic inflammation (Figure 2A). The endometrium was also replaced by HSIL, which involved the endometrial gland, squeezing into the superficial myometrium and forming SCC (Figure 2B). The bilateral adnexa were unremarkable, and there was no invasion of the nerves, lymph nodes or parametrium. Immunohistochemical staining was positive for p16 and Ki-67 expression in the cervix and endometrium (Figure 2C and D) and strongly positive for p63 expression in the endometrium (Figure 2E) but negative for vimentin and estrogen receptor in the endometrium (Figure 2F). The patient was finally diagnosed with cervical SCC stage IB and received radiotherapy. She was pleased to find that there were no signs of recurrence 1 year after surgery.

**DISCUSSION**

In 1900, Cullen first discovered a case of cervical SCC that spread to the entire endometrium; since then, only approximately 50 cases have been reported, with an occurrence of 0.7%[3]. Among these rare cases, although the endometrium is the most common site for metastasis, some cases revealed that the fallopian tubes and the ovaries could also be invaded[4]; the most distant site reported thus far is the omentum and the mucosa of the transverse colon[5]. Since the 1960s, scholars have discussed the potential risk factors that may contribute to upward metastasis, such as long-term estrogen usage, vitamin A deficiency, HPV infection, senile endometrium, pyometra, and radiotherapy[3]; among them, some have persisted until today, namely, advanced age, cervical stenosis and pyometra[6], and these are often the result of previous cervical procedures, such as LEEP or conization[5].

Astonishingly, we have found that some cases even shared the same characteristics as ours, for example, in a very recent case published in Spain, the 66-year-old patient also underwent cervical conization 15 years ago and had a finding of HSIL, was lost to regular follow-up, and underwent laparoscopic hysterectomy for the symptoms of vaginal discharge after discovering cervical stenosis and pyometra. Her final pathology also revealed HSIL within the cervix and SCC in the endometrium with a depth of 2.8 mm[7]. Anne Chao et al[8] also reported a case with fatal pyometra (1200 mL of pus that was cultured Staphylococcus epidermidis) in a 60-year-old patient whose pathology also revealed cervical HSIL that progressed into SCC in the endometrium. Therefore, it is reasonable to infer that these factors often interact with each other simultaneously, contributing to this rare disease. In postmenopausal women, cervical stenosis is easily formed after cervical treatment due to the loss of periodic abscission[9], and it encloses the uterine cavity and accelerates the pyometra (e.g., under inflammation). In time, the occult inflammatory environment within the uterus becomes a hotbed for a number of
diseases, namely, if a prior disease existed (a cervical lesion such as in our case), it may trigger the unusual cephalad spreading of the disease, or in other cases, it may be the cause of other diseases, such as the spontaneous rupture of the uterus[10], if there was no prerequisite for any other relevant diseases. Further studies should also be centered on the impact of this occult inflammatory microenvironment.

To date, there are two main theories explaining this unusual phenomenon: Horizontal theory and vertical theory. The horizontal theory proposes that the tumor originates from one stem cell of the cervix spreading upward to replace the benign cells[5]. The vertical theory proposes that the lesion occurs from a group of predetermined cells that are transformed into malignant cells simultaneously in a vertical direction[11]. In 2001, Kushima et al[4] reported 5 similar cases and explained this phenomenon on a genetic level. They found that even if the lesions are discontinuous between the cervix and endometrium, they still shared the same genetic alterations, which is generally the loss of heterozygosity frequently found on the 6p, 6q, 11p and 11q loci of the chromosome, thus supporting the horizontal theory that the SCC originates from one single cell and migrates upward while cloning itself.

Notably, this rare phenomenon should be distinguished from primary endometrial SCC (PESCC). PESCC is exclusively composed of cells with squamous differentiation. The diagnostic criteria for PESCC were established by Fluhmann[12] in 1953 and included the following: (1) No evidence of coexisting endometrial adenocarcinoma or primary cervical SCC; (2) No connection between the endometrial tumor and squamous epithelium of the cervix; or (3) No connection between any existing cervical in situ carcinoma and independent endometrial neoplasm.

As endometrial involvement of cervical SCC may be an indicator of poor prognosis[13] and is usually diagnosed after hysterectomy, early detection is of extreme significance. Many scholars emphasized the importance of evaluating the endometrium before hysterectomy was performed[14]. The key points included the thickness of the endometrium as well as whether there was unusual fluid in the uterine cavity; normally, these can be spotted with a pelvic ultrasound or an magnetic resonance imaging test. Endocervical curettage is also critical since a positive result may be an indication of a deeper lesion[5]. However, as shown in our case, even with all the aforementioned assistance, along with a thorough hysteroscopic exam, there is still an upgrade in the final diagnosis, which reveals the insidiousness of this disease and calls for more detection measurements in the future.

Prevention of this disease should be focused on minimizing recurrence in older patients who have undergone cervical procedures. A wider excision of the cervical lesion is often desired; however, this also increases the likelihood of cervical stenosis, which obscures the true condition of the cervix and thus increases the chances of relapse[9,15]. Although certain precautions, such as hormone therapy and urinary catheter stenting, are suggested[15], the follow-up of these patients is still challenging.

CONCLUSION

Upward spreading of cervical SCC/HSIL is rare, and advanced age, cervical stenosis, and pyometra are strong indications for this phenomenon. Pelvic ultrasound and hysteroscopy may help in early diagnosis, and better prevention depends on minimizing recurrence in older patients who have undergone prior cervical procedures. Since there are currently no guidelines for this specific entity and this condition may alter staging, more attention should be given to it.
Figure 2 Microscopic appearance of the disease. A and B: Hematoxylin–eosin staining of the cervix (A) and endometrium (B). While it was a high-grade squamous intraepithelial lesion in the cervix (blue arrow), the lesion penetrated into the endometrium and the myometrium, forming squamous cell carcinoma in the uterine cavity (orange arrow); C-F: Immunohistochemical staining of the uterus. Both the cervix (C) and endometrium (D) showed strong expression of p16 (arrow), p63 was also highly expressed in the endometrium (E), whereas expression of estrogen receptor was negative in the endometrium, and normal endometrial glands (arrow) could also be seen (F).

FOOTNOTES

Author contributions: Shu XY wrote the manuscript; Zhang D performed the surgery and was involved in the patient's direct care; Zhang S provided all the pathological images and revised the pathological part of the manuscript; Yang HX revised the manuscript; Bi H revised the manuscript critically for important intellectual content, and all authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for the publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors declare that they have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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REFERENCES


Type 2 autoimmune pancreatitis associated with severe ulcerative colitis: Three case reports

Mark Ghali, Karen Bensted, David B Williams, Simon Ghaly

BACKGROUND
Type two autoimmune pancreatitis is a rare and difficult to diagnose, steroid responsive non-IgG4 inflammatory pancreatopathy that can be associated with an aggressive course of ulcerative colitis. Clinician awareness about this condition is important to allow early diagnosis, treatment and avoid unnecessary pancreatic surgery.

CASE SUMMARY
This case series describes three cases with varied clinical presentations and representations of autoimmune pancreatitis, and all associated with an aggressive course of ulcerative colitis. The pancreatopathy was independent of bowel disease activity and developed in one case following colectomy.

CONCLUSION
Clinician awareness about this condition is important to allow early diagnosis, treatment and avoid unnecessary pancreatic surgery.

Key Words: Autoimmune pancreatitis; Inflammatory bowel disease; Ulcerative colitis; Colectomy; Case report

Core Tip: Type two autoimmune pancreatitis is a rare and difficult to diagnose, steroid responsive non-IgG4 inflammatory pancreatopathy that can be associated with an aggressive course of ulcerative colitis but with independence from bowel disease activity. Clinician awareness about this condition is important to allow early diagnosis, treatment and avoid unnecessary pancreatic surgery.
INTRODUCTION

The inflammatory bowel diseases (IBD), Crohn’s disease and ulcerative colitis (UC), are multisystem diseases that cause chronic relapsing inflammation within the gastrointestinal tract, and are associated with extraintestinal manifestations in up to 50% of patients[1]. Autoimmune pancreatitis (AIP) is one of the less recognised associations and remains poorly understood. AIP is a rare, fibro-inflammatory disease characterized by well-defined histopathological changes with an unclear pathogenesis[2]. The annual incidence rate has been reported between 0.29 to 1.4 per 100000 population, with a prevalence rate up to 4.6 per 100000 population[3,4]. Two distinct types have been described: Type one AIP (lymphoplasmacytic sclerosing pancreatitis), which is considered the pancreatic manifestation of IgG4-related disease, and type two AIP (idiopathic duct centric pancreatitis) which has been associated with inflammatory bowel disease[5].

The diagnosis of type 2 AIP is based on the International Consensus Diagnostic Criteria (ICDC), which combines clinical, imaging and histological findings (Table 1). The criteria acknowledge the level of uncertainty in diagnosing type 2 AIP by having criteria for definitive and probable diagnoses, these are summarized in Table 2. Of relevance the diagnostic requirements in patients with a clinical diagnosis of inflammatory bowel disease are less stringent. Probable type 2 AIP requires level 1 or 2 imaging evidence and a response to steroids; definitive type 2 AIP requires level 1 or 2 imaging evidence and level 1 or 2 histology and a response to steroids[6]. In clinical practice, acquiring adequate tissue by endoscopic ultrasound guided biopsy of the pancreas is difficult, particularly given granulocytic epithelial lesions can have a patchy distribution[7]. Distinguishing AIP from other malignant and non-malignant diagnoses is essential given the marked differences in prognosis and treatment.

Here we present three cases of patients with UC presenting with severe pancreatopathies from a single centre tertiary hospital IBD unit. Each case demonstrated unique clinical features, however were similar in their severe course of IBD. A summary of the cases has been included in Table 3.

CASE PRESENTATION

Chief complaints

Case 1: A 57-year-old man presented with the onset of scleral icterus and jaundice over a 3-day period.

Case 2: A 62-year-old man presented with jaundice.

Case 3: A 46-year-old female presented with epigastric pain.

History of present illness

Case 1: The patient had one month of lethargy preceding his acute presentation with jaundice.

Case 2: The patient’s jaundice was associated with epigastric pain and 8 kg weight loss.

Case 3: The patient had mild distal UC diagnosed one month earlier treated with mesalazine suppositories.

History of past illness

Case 1: Past medical history included a non-significant alcohol history and UC diagnosed 3 years earlier and requiring subtotal colectomy with ileostomy soon after diagnosis due to acute severe colitis failing rescue therapy. Following surgery the patient was off all medical therapy.

Case 2: Past medical history included a non-significant alcohol history, prior cholecystectomy and longstanding ulcerative pancolitis in clinical remission without ongoing medical therapy.

Case 3: Past medical history included no significant alcohol history, iron deficiency anaemia, HSV type 2 infection, and recurrent pneumothoraces requiring pleurodesis and pleurectomy.

Laboratory examinations

Case 1: Bloods demonstrated a mixed pattern of liver function test derangements: Bilirubin 64 μmol/L
Table 1 Diagnostic criteria for type 2 autoimmune pancreatitis

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Level 2</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>A response to a steroid trial with rapid (&lt; 2 wk) radiologically demonstrable resolution or marked improvement in manifestations</td>
</tr>
<tr>
<td>Parenchymal imaging</td>
<td>Diffuse enlargement with delayed enhancement</td>
</tr>
<tr>
<td>Ductal imaging</td>
<td>Long (&gt; 1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation</td>
</tr>
<tr>
<td>Histology</td>
<td>Granulocytic infiltration of duct wall, granulocytic epithelial lesions with or without granulocytic acinar inflammation and; absent or scant (0-10 cells/HPF) IgG4-positive cells</td>
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Table 2 Diagnosis of definitive and probable type 2 autoimmune pancreatitis

<table>
<thead>
<tr>
<th>Imaging evidence</th>
<th>Collateral evidence</th>
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<td>Probable Level 1 or 2</td>
<td>Level 2 histology OR; IBD and response to steroids</td>
</tr>
<tr>
<td>Definitive Level 1 or 2</td>
<td>Level 1 histology OR; IBD, level 2 histology and response to steroids</td>
</tr>
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</table>

OR: Odds ratio; IBD: Inflammatory bowel diseases.

Table 3 Case summaries

<table>
<thead>
<tr>
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<th>Case 2</th>
<th>Case 3</th>
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<td>Extent of UC (Montreal)</td>
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<td>A3 E3</td>
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<td>Extraintestinal manifestations</td>
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<td>Occurrence of cancers</td>
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<td>Age at AIP diagnosis</td>
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<td>Other organ involvement</td>
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</tr>
<tr>
<td>Presentation</td>
<td>Obstructive jaundice</td>
<td>Obstructive jaundice</td>
</tr>
<tr>
<td>IBD or AIP first</td>
<td>IBD</td>
<td>IBD</td>
</tr>
<tr>
<td>Treatment</td>
<td>Corticosteroids</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Relapse</td>
<td>Yes (spontaneous resolution)</td>
<td>Nil</td>
</tr>
<tr>
<td>Evolution (diabetes, exocrine insufficiency)</td>
<td>Diabetes</td>
<td>Diabetes, Exocrine insufficiency</td>
</tr>
</tbody>
</table>

IBD: Inflammatory bowel diseases; UC: Ulcerative colitis; AIP: Autoimmune pancreatitis.

(0-18), ALT 1200 U/L (0-30), AST 458 U/L (0-30), ALP 999 U/L (30-100), GGT 2180 U/L (0-35) with bilirubin soon peaking at 151 μmol/L. A random blood sugar level was elevated to 15 mmol/L (4.0-7.8) with no history of diabetes. HbA1c was 7.0% (0-5.9). Serum CA 19.9 47kU/L (0-34 kU/L) and IgG4 0.58g/L (0.04-1.64g/L).

Case 2: Blood tests demonstrated bilirubin 200 μmol/L (4-20), AST 118 U/L (10-40), ALT 284 U/L (5-40), ALP 169 U/L (35-110), GGT 792 U/L (5-50), and hyperglycaemia with BGL 14 mmol/L (4.0-7.8) with no prior history of diabetes. Serum CA 19.9 was non-specifically elevated to 62 kU/L (< 40), triglycerides normal 2.1 mmol/L (0.5-2) and IgG4 Levels were normal 0.69 g/L (0.04-1.64). Subsequent CA 19.9 were 51 and 15 kU/L, 3 wk and 2 mo later, respectively.
Case 3: Bloods showed an elevated lipase 518 U/L (8-78). Serum triglycerides 0.7 mmol/L (< 2.0) and IgG4 were not elevated 0.38 g/L (0.04-0.86).

Imaging examinations

Case 1: Computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) demonstrated intra and extrahepatic bile duct dilatation with a transition point at the distal common bile duct, although no pancreatic mass was identified. No supporting features of primary sclerosing cholangitis. There was diffuse diffusion restriction involving the pancreatic head, neck and proximal body, suspicious for autoimmune pancreatitis. Findings on contrast enhanced endoscopic ultrasound (CE-EUS) and fludeoxy glucose-positron emission tomography/CT (FDG-PET/CT), were also consistent with this – with diffusely increased tracer activity within the pancreas suggestive of an inflammatory process rather than malignancy (Figure 1A), and diffusely abnormal pancreas on CE-EUS with heterogeneous honeycombed appearance, and atrophy of the pancreatic tail.

Case 2: Multiphasic CT abdomen and MRCP demonstrated mild thickening and oedema of the head and body of the pancreas with subfe effacement of the peri-pancreatic fat planes, with associated intra and extrahepatic biliary dilatation with a common bile duct of 9 mm and abrupt cut off within the pancreatic head, raising concern of malignancy (Figures 2 and 3). CE-EUS however demonstrated a diffusely hypoechoic pancreas with no distinct mass lesion. The pancreas was uniformly hypervascular with no discrete area of altered microvascular flow in the head of the pancreas.

Case 3: Abdominal ultrasound excluded cholelithiasis. CT abdomen showed features of mild pancreatitis. MRCP demonstrated changes of pancreatitis with mild oedema of the tail of pancreas associated with minimal peripancreatic stranding, but no mass or cystic lesions of the pancreas.

Considering the remote possibility of mesalazine suppositories causing pancreatitis, this was switched to prednisolone suppositories. Despite this, over the subsequent months the patient experienced ongoing pain, reduced appetite, weight loss and ultimately required hospitalization. FDG-PET/CT revealed mild to moderate avidity in the whole pancreas.

FINAL DIAGNOSIS

Probable type 2 autoimmune pancreatitis associated with severe ulcerative colitis was the diagnosis in each case at this point. However, with case three, a definitive diagnosis was made following further investigation as will be discussed below.

TREATMENT

Case 1
Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated a tight 3.5 cm distal biliary stricture, with non-diagnostic bile brushings and a plastic stent was inserted for biliary drainage. Duodenal biopsy revealed duodenitis with 3 IgG4 positive plasma cells per high power field with an IgG4/IgG of 5% (fewer than the > 10 required to diagnose IgG4 disease). Based on multimodal imaging and EUS findings, a diagnosis of probable type 2 AIP was considered, and treatment commenced with prednisolone 40mg tapered over eight weeks.

Case 2
ERCP demonstrated a 2 cm smooth stricture in the distal CBD with a dilated proximal duct of 9 mm, no additional intra- or extrahepatic biliary strictures were noted to suggest primary sclerosing cholangitis which was deemed unlikely given the diffuse pancreatic changes on imaging. Bile duct brushing were taken and demonstrated benign biliary epithelium. A 7 cm plastic biliary stent was placed. To confirm the benign nature of the biliary stricture, balloon cholangioscopy was subsequently performed and a fully covered self-expanding metal stent (SEMS) was inserted. This was able to be successfully removed 6 mo later. Based on CE-EUS and imaging findings, a diagnosis of probable type two AIP was considered and a steroid trial commenced with prednisone 30 mg daily tapered over 8 wk, pancreatic enzyme supplementation for pancreatic insufficiency, and supplemental insulin for new-onset diabetes. There was no recurrence of pancreatitis or jaundice after completing the steroid taper.

Case 3
Based on the above investigations type 2 AIP was considered probable and a tapering trial of prednisone 40 mg over 8 wk commenced.
OUTCOME AND FOLLOW-UP

Case 1
A repeat FDG-PET/CT following steroid treatment demonstrated complete resolution of FDG uptake (Figure 1B). The benign stricture required sequential plastic stenting, which were subsequently removed after six months. Eighteen months later, the patient developed acute pancreatitis presenting with epigastric abdominal pain, elevated CRP (174 mcg/mL) and lipase (360 U/L), which resolved with conservative measures. CT and ultrasound showed features of pancreatitis but excluded cholelithiasis.
and there was no biliary dilatation. The patient went on to have completion proctectomy which was uncomplicated and has remained well 24 mo after this episode with no further pancreatitis or need for immunosuppression.

**Case 2**
Three months after the initial episode of jaundice, the patient experienced an episode of acute severe ulcerative colitis requiring IV hydrocortisone and rescue therapy with infliximab. He remained in clinical remission for 6 mo on combination therapy with infliximab, azathioprine and allopurinol but subsequently had secondary loss of response to dose optimized infliximab, vedolizumab and tofacitinib. He ultimately came to colectomy three years after his pancreatitis diagnosis. There was no recurrence of pancreatitis subsequently.

**Case 3**
Symptoms ultimately improved slowly over the subsequent month, however relapsed once a prednisolone dose of 15 mg was reached. Repeat FDG-PET/CT revealed improvement in the degree of FDG uptake but ongoing activity in the pancreatic head and uncinate process. CE-EUS with fine needle biopsy was performed. This showed abnormal pancreatic parenchyma that was honeycombed and lobular in the head and neck of the pancreas. Within the uncinate there was a 17 mm focal hypoechoic area that was targeted for fine needle biopsy. The histopathology demonstrated lymphocytic acinar inflammation and features suggestive of granulocytic acinar infiltrate, which could be consistent with type 2 AIP (Figure 3). There were no pancreatic ducts present in the specimen, therefore duct centric inflammation or the presence of granulocytic epithelial lesions could not be assessed. No plasma cells were seen, and thus the tissue was presumably absent of IgG4-positive cells. Symptoms were managed with regular analgesia and pancreatic enzyme replacement due to the patients’ reluctance for further steroid therapy.

Three months later, the patient developed acute severe UC with disease extension to the descending colon. She was treated with intravenous hydrocortisone, and subsequently rescue therapy with infliximab followed by ciclosporin after declining colectomy and a lack of response to infliximab. A partial response to ciclosporin was observed and allowed transition to vedolizumab with improvement in symptoms. She has remained in clinical remission with 12 mo of follow up with no relapse of pancreatitis or ulcerative colitis on maintenance vedolizumab 4-weekly infusions.

**DISCUSSION**

The presentation of AIP in the setting of IBD is variable with one study showing 80% presenting with acute pancreatitis, 11% with abdominal pain, 7% with jaundice and 2% being incidentally detected. Of note in the GETAID-AIP study, 98% of those with IBD and AIP, had type 2 AIP illustrating the relationship with IBD being more specific to type 2 AIP[8]. Our case series demonstrated the varied clinical presentations of AIP, with obstructive jaundice in two, and acute pancreatitis in one. Of interest, patients did not necessarily relapse with the same clinical presentation, with case one initially presenting with jaundice and subsequently presenting with abdominal pain.

Autoimmune pancreatitis in the setting of IBD is challenging to diagnose but a clinically important entity to recognize and treat accordingly. The cases presented highlight a unique phenotype of both severe pancreatopathy and severe IBD. Despite this, they do not easily fit the published diagnostic criteria of AIP despite multiple diagnostic investigations. This is consistent with findings from the GETAID case series where only 16% of IBD associated pancreatitis met definitive type 2 AIP criteria[8]. In our cases, 2 met the criteria for probable type 2 AIP based on imaging findings (level 1 or 2), clinical diagnosis of IBD and response to steroids. The third case met criteria for definitive type 2 AIP based on supportive imaging findings (level 2), level 2 histology with clinical IBD and response to steroids. It is important to note the diagnostic criteria for response to steroids is based on either radiologically demonstrable resolution or marked improvement in manifestations within 2 wk, with radiological confirmation likely to be more useful in the context of uncertainty regarding potential malignancy[6]. Due to several reasons, response to steroids was not assessed after 2 wk by repeat imaging in these cases: firstly, there was thorough initial multimodal evaluation to exclude malignancy; secondly, improvement in jaundice, pain or liver enzymes were consistent with steroid response and; lastly, there were practical challenges regarding access to care for two out of three patients who lived in rural areas > 500 km from the treating centre.

There are no published guidelines for investigating suspected autoimmune pancreatitis in the setting of IBD, which is relevant as the pre-test probability for a positive diagnosis is likely to be higher than the general population. The ICDC for type 2 AIP, emphasise the need for pancreatic core biopsy early in the course of investigation, but this may not be the case in the setting of IBD[6]. In the presented cases FDG-PET/CT and CE-EUS were included in the diagnostic evaluation. A diagnostic steroid trial is suggested to determine if there is rapid radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations[6]. While steroid response does not differentiate type 1 from
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Figure 4 Suggested diagnostic algorithm for autoimmune pancreatitis in inflammatory bowel diseases. IBD: Inflammatory bowel diseases; AIP: Autoimmune pancreatitis; CT: Computed tomography; MRI: Magnetic resonance imaging; FDG-PET: Fludeoxy glucose-positron emission tomography; CE-EUS: Contrast enhanced endoscopic ultrasound.

type 2 AIP, it is supportive evidence of a form of AIP. An incomplete clinical response to steroids or relapse on a weaning dose, however, may incorrectly steer the diagnosis away from AIP or alternatively a trial of steroids may delay the diagnosis of malignancy. As such, a two weeks trial of steroids followed by assessing the response has been suggested in carefully selected patients[2]. This is highlighted in case three, where the clinical improvement on the initial course of prednisone was short lived, however FDG-PET/CT demonstrated diffuse uptake throughout the pancreas at baseline with definite improvement post steroids. Diffuse uptake of FDG in the pancreas and the ratio of pancreatic lesion/liver, salivary gland and prostate standardized uptake values (SUV) thresholds have been suggested by others to favor but not definitively diagnose AIP[9]. Caution needs to be taken with focal compared to diffuse abnormalities that improve with corticosteroids, as this can also be seen with malignancy.

In cases where there is a focal pancreatic lesion, use of CE-EUS may help distinguish AIP from pancreatic cancer and justify a trial of steroids. On CE-EUS, AIP demonstrates hyper to iso enhancement in the arterial phase, homogenous contrast agent distribution and absent irregular internal vessels[10]. Thus, CE-EUS can be used to aid the diagnosis of AIP by decreasing the likelihood of a cancer diagnosis whilst justifying the use of a steroid trial. EUS also offers the opportunity for pancreatic biopsy at the same procedure. The utility of histological acquisition in diagnosis was demonstrated in case three where biopsy excluded malignancy and demonstrated changes suggestive of type 2 AIP[11]. Therefore, considering our cases and the modalities of FDG-PET/CT and CE-EUS, one possible strategy could include performing FDG-PET/CT scans, followed by CE-EUS with or without biopsy depending on clinical suspicion, to determine utility of a trial of steroids. We have incorporated this into a suggested diagnostic algorithm shown in Figure 4. The diagnostic accuracy and cost-effectiveness of this strategy
requires investigation.

The presence of autoimmune pancreatitis in UC may indicate a more severe phenotype of IBD. This is supported by the largest case series looking at AIP and UC by the GETAID-AIP study group, with a statistically significant increase in colectomy rate in patients with IBD and AIP compared to those that had IBD without AIP[8]. In two of our three cases, the patients required colectomy. This suggests a unique phenotype of IBD patients with genetic predisposition to AIP and aggressive IBD. In the GETAID-AIP study, of the 18 patients who underwent a colectomy, seven had a colectomy prior to a diagnosis of AIP. This can be seen in case one of our series, where the diagnosis of AIP occurred after their colectomy. In case two, the patient’s colitis was quiescent until the diagnosis of autoimmune pancreatitis. However, once the patient developed AIP, he had a deterioration in the severity of his IBD, and ultimately required a colectomy. These findings suggest that it is not necessarily active IBD or the colonic microbiome causing the autoimmune pancreatitis, rather it may be genetic, immunological or systemic inflammatory mechanisms causing the disease, with further research required into its pathogenesis.

CONCLUSION

Autoimmune pancreatitis in the setting of IBD, is a rare and difficult to diagnose, steroid responsive non-IgG4 inflammatory pancreatopathy that does not easily fit the current diagnostic criteria for type 1 or 2 autoimmune pancreatitis and likely represents a separate entity. This case series describes three cases with varied clinical presentations and re-presentations of autoimmune pancreatitis, and all associated with an aggressive course of inflammatory bowel disease. Novel diagnostic tools such as FDG-PET and contrast enhanced EUS may play a role in the evaluation of this condition. Clinician awareness about this condition is important to allow early diagnosis and appropriate therapy.

ACKNOWLEDGEMENTS

Histology images courtesy of: Dr Sharron Liang, Postgraduate Molecular Fellow – Anatomical Pathology and Precision Medicine and Associate Professor Tao Yang, Consultant in Anatomical Pathology and Molecular Pathology; SydPath, St. Vincent’s Hospital.

FOOTNOTES

Author contributions: Williams DB and Ghaly S created the report design; Ghali M performed case note review and manuscript drafting; Ghali M, Bensted K, Williams DB and Ghaly S performed manuscript editing.

Informed consent statement: The written Informed consent was obtained from all patients.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wang DM
L-Editor: D
P-Editor: Wang DM
REFERENCES


CASE REPORT

Diffuse uterine leiomyomatosis: A case report and review of literature

Hui-Min Ren, Qing-Zhu Wang, Jia-Nan Wang, Gang-Jie Hong, Shuang Zhou, Jun-Yan Zhu, Shan-Ji Li

BACKGROUND

Diffuse uterine leiomyomatosis (DUL) is a benign uterine smooth muscle neoplasm with unknown etiology. Since DUL is rarely reported, knowledge regarding it is limited. The rate of early diagnosis is low, and DUL is often misdiagnosed as common multiple uterine leiomyomas before surgery.

CASE SUMMARY

A 27-year-old patient with no sexual activity presented to the Emergency Department of our hospital complaining of heavy vaginal bleeding. She had a history of uterine fibroids and menorrhagia. Pelvic examination showed a regularly enlarged uterus, similar in size to that associated with a 4-mo pregnancy. Pelvic magnetic resonance imaging (MRI) revealed numerous multiple uterine fibroids, and a transabdominal myomectomy (TM) was performed. Intraoperative exploration revealed that the myometrium was full of myoma nodules of variable sizes. Over 50 leiomyomas were removed. The pathology report confirmed leiomyoma. The patient was discharged and received a gonadotropin-releasing hormone analog (3.75 mg) for 6 mo. Ten months after surgery, the patient presented to the hospital again for abnormal uterine bleeding. MRI showed an irregular mass with a diameter of 5.2 cm without sharp demarcation in....
the uterine cavity. Submucosal leiomyoma was considered first, and the patient underwent a hysteroscopic myomectomy plus hymen repair. Intraoperative exploration showed that there were several leiomyomatosis masses in the cavity. Postoperative pathological examination confirmed submucosal leiomyoma and necrotic and generative tissue. Although the menstrual cycle was still irregular, the patient did not have symptoms of menorrhagia for a period of 28 mo after the second surgery.

**CONCLUSION**

Individuals with DUL are easily misdiagnosed due to the lack of specific manifestations of this disease. MRI is helpful for early identification and preoperative evaluation. There is currently no unified method of diagnosis. For women who want to preserve fertility, conservative surgery should be made an option. When TM is chosen, a modified new myomectomy should be considered to avoid the drawbacks of traditional TM.

**Key Words:** Diffuse uterine leiomyomatosis; Leiomyoma; Myomectomy; Uterine-sparing surgery; Case report

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**Core Tip:** Diffuse uterine leiomyomatosis (DUL) is a benign uterine smooth muscle neoplasm with unknown etiology. Hysterectomy is the only curative therapy. We report a 27-year-old female with no sexual activity who was diagnosed with DUL. The patient was misdiagnosed with leiomyoma preoperatively, followed by treatment with transabdominal myomectomy (TM), a gonadotropin-releasing hormone analog, and hysteroscopic myomectomy plus hymen repair. This case highlights the importance of pelvic magnetic resonance imaging as a diagnostic tool. For women who want to preserve fertility, conservative surgery should be an option. When TM is chosen, a modified new myomectomy should be considered to avoid the drawbacks of traditional TM.


**URL:** https://www.wjgnet.com/2307-8960/full/v10/i24/8797.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i24.8797

**INTRODUCTION**

Diffuse uterine leiomyomatosis (DUL) is a benign and rare uterine smooth muscle neoplasm. It was first reported by Murray and Glynn [1] in 1924 and described as “complete uterine fibromyomatosis”. It was then named DUL by Lapan and Solomon [2] in 1979. It presents mainly in young women of childbearing age. Since DUL is rare and has not been widely reported, knowledge regarding it is limited. The rate of early diagnosis is low, and DUL is often misdiagnosed as common multiple uterine leiomyomas before surgery. Total abdominal hysterectomy is the main treatment for DUL [3,4]. However, considering the early age of onset, preserving reproductive function has become the focus of treatment. At present, there is no unified standard treatment at home or abroad. We report a case of DUL in which the uterus was successfully retained during treatment and review the literature.

**CASE PRESENTATION**

**Chief complaints**
A 27-year-old patient presented to the Emergency Department of our hospital complaining of heavy vaginal bleeding.

**History of present illness**
The patient’s symptoms started half a month prior and were accompanied by dizziness.

**History of past illness**
The patient was diagnosed with multiple uterine myomas via an ultrasound scan in 2015. Given the age and normal menses amounts, her family chose a follow-up observation at that time. Her usual
menstrual cycle was 30-45 d with moderate bleeding lasting 7 d with clots and dysmenorrhea. However, since 2017, her menstrual period has changed to 10-15 d of heavy bleeding. She also sometimes felt dizzy and fatigued. Her lowest hemoglobin concentration was 32 g/L. She was not sexually active.

**Personal and family history**
The patient’s mother underwent an abdominal hysterectomy for uterine fibroids at the age of 40. The patient’s aunt (her father’s sister) had a history of uterine fibroids without surgery. The pedigree of this family is shown in Figure 1.

**Physical examination**
Pelvic examination showed a regularly enlarged uterus, similar to the size at 4 mo of pregnancy, with a hard texture.

**Laboratory examinations**
Blood analysis revealed moderate anemia, with a hemoglobin level of 52 g/L. Serum tumor markers (CA125, CA199, CEA, AFP, SCC) were normal.

**Imaging examinations**
Ultrasound showed that the volume of the uterus was significantly increased. The size of the uterus was approximately 13 cm × 9.2 cm × 11 cm, and the myometrium and uterine cavity were full of numerous hypoechoic masses of variable sizes. Pelvic magnetic resonance imaging (MRI) was performed one month later and revealed numerous multiple uterine fibroids (Figure 2A and B).

**FINAL DIAGNOSIS**
The final diagnosis was DUL, which was made after the operation.

**TREATMENT**
In the emergency room, the patient received ethinylestradiol and cyproterone acetate to stop bleeding and iron supplements to improve anemia. The patient was admitted two months later and underwent transabdominal myomectomy (TM). Intraoperative exploration revealed an enlarged uterus similar to that at 5 mo of pregnancy and normal adnexa. The myometrium was full of myoma nodules of different sizes. The largest nodule was 5 cm in diameter, and the smallest was 0.8 cm in diameter. An abundant blood supply was noted. To reduce intraoperative bleeding, a soft catheter was used as a uterine artery tourniquet at the uterine isthmus level (a tourniquet hole was made in the transparent area of the anterior and posterior lobe of the broad ligament, and a pea clip was inserted). Six units of vasopressin were injected into the uterine body, and 20 units of oxytocin were administered continuously via an intravenous drip during the operation. Over 50 leiomyomas were removed. The total operative time was 220 min. Despite the measures for bleeding prevention, intraoperative bleeding was up to 1800 mL, and 4 units of red blood cells and 400 mL plasma were transfused. The pathology report revealed leiomyoma (Figure 3). The patient was discharged and received 3.75 mg of gonadotropin-releasing hormone analog (GnRHa) for 6 mo. Ultrasonography at the follow-up visit revealed that the size of the uterus had decreased to 8.4 cm × 7.4 cm × 7.1 cm after GnRHa treatment.

The patient presented to the hospital for abnormal uterine bleeding 10 mo following surgery. MRI showed an irregular mass with a diameter of 5.2 cm without sharp demarcation in the uterine cavity. Submucosal leiomyoma was considered first (Figure 2C and D). Hysteroscopic myomectomy (HM) plus hymen repair was performed 11 mo after the first surgery. Intraoperative exploration showed that the depth of the cavity was 9 cm. There were several leiomyomatosis masses that measured from 1 to 2.6 cm in diameter in the cavity and a yellowish-brown abnormal growth 2 cm in diameter in the uterine fundus. The ostia of both fallopian tubes were clear. Postoperative pathological examination confirmed submucosal leiomyoma and necrotic and generative tissue.

**OUTCOME AND FOLLOW-UP**
Although the menstrual cycle was still irregular (7-8/30-60 d), the patient had a 28-mo postoperative follow-up, and her symptoms of menorrhagia were resolved. Pelvic MRI at the last follow-up showed that the shape of the uterus was irregular, the myometrium was uneven, and the endometrium was slightly thickened (Figure 2E and F).
Figure 1 Pedigree diagram of the family.

DISCUSSION

We report a 27-year-old female with no sexual activity who was diagnosed with DUL. The patient was misdiagnosed with leiomyoma preoperatively, followed by treatment with TM, GnRHa, and HM plus hymen repair.

The etiology of DUL is unclear. Currently, it is considered multiple leiomyomata of a hyperactive state. Baschinsky et al.[5] performed a clonality analysis of several lesions in one patient. All foci showed nonrandom X-chromosome inactivation, while different foci had different inactivated X-chromosomes, suggesting that the cells in one focus were from a monoclonal origin and those from different foci were polyclonal. The gross appearance of DUL is a symmetrically enlarged uterus. The diffusely thickened myometrium was almost completely crowded with innumerous solid, weakly defined confluent nodules ranging from 2 to 30 mm in diameter[2,6]. However, in the presented case, the maximum

Figure 2 Pelvic magnetic resonance imaging T2-weighted images before and after operations. A: Sagittal section before transabdominal myomectomy (TM); B: Coronal section before TM; C: Sagittal section before hysteroscopic myomectomy (HM); D: Coronal section before HM; E: Sagittal section after HM; F: Coronal section after HM.
diameter of the nodule was up to 50 mm. To the best of our knowledge, the presented case is the first to describe a nodule with a diameter up to 50 mm. This indicates that DUL lesions should not be limited to 30 mm. Histopathologic examination of DUL lesions reveals hypercellular and shorter smooth muscle cells arranged irregularly and/or compactly. Cellular pleomorphism and abnormal mitotic figures are absent. Vascular invasion is also negative[7]. Immunohistochemical staining of the progesterone receptor (PR) and the estrogen receptor (ER) is usually higher in a myoma than in adjacent myometrium, while the expression of Ki-67 is not different. The expression in DUL shows that PR in nodules is significantly higher than that in the surrounding normal myometrium, and ER and Ki-67 do not differ between these two tissues[8]. The rapid growth of DUL lesions and intralesional bleeding after the use of clomiphene and norethisterone have been reported[9]. The immunohistochemical results of our patient were entirely consistent with those of DUL, and the enlargement of the lesions in a short time may correlate with ethinylestradiol and cyproterone acetate treatment.

Clinical symptoms and ultrasound findings associated with DUL lesions are similar to those of uterine leiomyoma and lack specificity[10]. MRI, due to its high resolution of soft tissue, is helpful for early identification and preoperative evaluation. It reveals symmetrical and uniform enlargement of the uterus with innumerable and ill-defined myomas of different sizes in the myometrium and uterine cavity[10]. The differential diagnosis of a diffusely enlarged uterus with countless fibroid nodules includes hereditary leiomyomatosis and renal cell carcinoma (HLRCC) and Alport syndrome with diffuse leiomyomatosis (ASDL). HLRCC is an autosomal dominant disorder caused by mutations of the FH gene. Cutaneous leiomyoma is usually the first manifestation, concomitant with multiple uterine leiomyomas and renal cell carcinoma[11]. ASDL is an X-linked inherited disorder that results from distinct mutations in the COL4A5 gene. Myoma lesions are widely spread over the esophagus, trachea, bronchi, and genitalia[12].

Due to its rarity, preoperative misdiagnosis of DUL is common, and the diagnosis is largely dependent on preoperative MRI and postoperative pathology, which means that initially, the patients are treated inappropriately. The mother of the patient in this case underwent a hysterectomy at 40 years of age for multiple myomas. If the diagnosis of DUL is confirmed, the occurrence of DUL may result from complex genetic factors. Thus, the genetic mechanism of DUL should be further studied.

To date, the most effective treatment for DUL is total hysterectomy. However, considering that it is common in young women of reproductive age, gynecologists are working to identify appropriate methods to preserve reproductive function for those who desire fertility[6]. Medical and conservative surgeries include the use of GnRHa[13], HM[14-17], uterine artery embolization (UAE)[18,19], high-
intensity focused ultrasound (HIFU) ablation\textsuperscript{[20]}, and TM. Successful pregnancies after GnRHa, HM, UAE, and combined treatment have been reported\textsuperscript{[21]}. HIFU ablation has been demonstrated to be effective in controlling the symptoms of DUL\textsuperscript{[22]}. However, TM is the most commonly used therapy. Nevertheless, there are many disadvantages to traditional TM. Traditional TM can lead to massive intraoperative bleeding, intrauterine adhesions, incomplete clearance, and recurrence after surgery.

Therefore, several new types of myomectomy have been attempted over the last decade. Generally, these strategies share the same critical steps: (1) Longitudinal midline incisions penetrating through both the anterior and posterior full uterine walls are made; (2) As many leiomyomas as possible are removed from the incision; and (3) The incision is closed in three layers with absorbable sutures. In addition, hormonal treatment before surgery is recommended. The average amount of blood lost is 1437 g (range, 428-4421 g), and the average operation time is 271 min (range 180-407 min). In studies of the new myomectomy technique, five patients became pregnant, with four undergoing cesarean section. Regrettably, the fifth pregnancy ended in miscarriage. No uterine rupture was reported\textsuperscript{[23-25]}. For patients with fertility requirements, GnRHa should be considered as the initial therapy. When it fails, HM could be an option to restore as much morphology of the uterine cavity as possible. Repeated surgery with damage to the endometrium should be avoided. To avoid recurrence, patients should try to have children as early as possible postoperatively, and assisted conception techniques can be used when necessary\textsuperscript{[26]}. Our patient was misdiagnosed with multiple uterine fibroids before the operation, and because of her asexual life history, traditional TM was performed. Despite the steps taken to reduce bleeding, intraoperative bleeding reached 1800 mL. Weak uterine contractions, extensive uterine incisions secondary to misdiagnosis and incomplete preoperative preparation were the main reasons for bleeding. In a Cochrane meta-analysis, Thubert et al\textsuperscript{[27]} found that GnRHa therapy before myomectomy significantly reduced fibroid volume and improved postoperative hemoglobin levels. Taken together with the 5 cases of patients treated with the new technique and pretreatment, GnRHa therapy prior to myomectomy is effective in reducing hemorrhage in patients with uterine fibroids and those with DUL. The administration of GnRHa before myomectomy in patients who have numerous lesions and a massive uterus might minimize the complications of misdiagnosis.

Although a total of 6 cycles of GnRHa were administered postsurgery, menorrhagia recurred approximately 10 mo after TM. HM and hymen repair were performed after receiving informed consent. To date, the patient has recovered well with no return of her symptoms. The cause of her recurrent heavy bleeding was attributed to residual disease. The anterior and posterior full uterine walls were not cut open, and the whole uterine cavity was not exposed completely during the operation. The disadvantage of TM was then partly compensated by HM.

Although DUL is a benign condition, it may exhibit parametrial, ovarian, mesenteric, and bone metastasis in rare cases\textsuperscript{[28-30]}. After hysterectomy and removal of metastatic lesions, no recurrence has been reported\textsuperscript{[22]}. Even without the treatment of multiple metastatic lesions in bones, they completely regressed after hysterectomy\textsuperscript{[22]}.

**CONCLUSION**

DUL is easily misdiagnosed as multiple uterine leiomyomas. Thus, it is necessary to consider DUL in this situation. Improvement in ultrasound technology and the popularization of preoperative MRI for multiple uterine fibroids are beneficial to the early diagnosis of DUL. Hysterectomy is the only cure for DUL. For women who want to preserve fertility, a deliberate choice of conservative surgery should be made. When TM is chosen, a new modified myomectomy should be considered to avoid the drawbacks of traditional TM.

**FOOTNOTES**

**Author contributions:** Ren HM and Wang QZ contributed equally to this work; all authors contributed to the design and conduct of the study and approved the submission of this work for publication.

**Informed consent statement:** Informed consent was obtained from the patients for participation in this study and the publication of the results.

**Conflict-of-interest statement:** None of the authors have any conflicts of interest to report.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Comment on “Posterior reversible encephalopathy syndrome in a patient with metastatic breast cancer: A case report”

Suljo Kunić, Omer Ć Ibrahimagić, Biljana Kojić, Dževad Džananović

Posterter reversible encephalopathy syndrome (PRES) is a neurotoxic encephalopathic state, manifesting clinical symptoms of headache, altered consciousness, visual disturbances, and seizures. Although several diseases have been identified as causative of PRES, the underlying mechanism remains unclear. Song et al recently published “Posterior reversible encephalopathy syndrome (PRES) in a patient with metastatic breast cancer: A case report” in the World Journal of Clinical Cases, highlighting and discussing the role of hypercalcemia in PRES as related to uncontrolled hypertension. To build upon this case description, we provide further insight into the possible underlying mechanisms of PRES through this commentary.

Key Words: Case report; Hypercalcemia; Paraneoplastic syndrome; Posterior reversible encephalopathy syndrome

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Core Tip: We speculate that posterior reversible encephalopathy syndrome may be caused by paraneoplastic antibodies, tumors or even antitumor therapy, per se, in addition to the hypercalcemia postulated by Song et al in “Posterior reversible encephalopathy syndrome (PRES) in a patient with metastatic breast cancer: A case report” (World Journal of Clinical Cases, March 2022).
TO THE EDITOR

We read the article “Posterior reversible encephalopathy syndrome (PRES) in a patient with metastatic breast cancer: A case report”, written by colleagues Song et al[1] and published in the March online issue of World Journal of Clinical Cases, with great interest. We now welcome the opportunity to make a short comment, as this very interesting article assumes the role of hypercalcemia in PRES by causing uncontrolled hypertension.

With regard to the 51-year-old woman with PRES-related hypercalcemia described in the Case Report, we agree with authors’ insight that there are various possible causes of the neurological symptom of high-level serum calcium. In a similar Case Report by Mirian et al[2], a 74-year-old woman with PRES is described with elevations in serum calcium associated with this syndrome; her imaging abnormalities completely resolved after the serum calcium returned to normal. There is also the case of a 38-year-old woman with breast tumor reported by Camara-Lemarroy et al[3]; for this patient, the treating physicians considered the physiopathological mechanisms of malignant hypercalcemia (14.5 mg/dL) that can lead to neurological symptoms corresponding to PRES. Ultimately, all 3 cases support the role of hypercalcemia in PRES.

However, Barber et al[4] have clinical experience with PRES presenting in a 58-year-old woman with ovarian cancer in the presence of paraneoplastic antibodies (namely, antibodies to collapsin response-mediator protein-5), detected in cerebrospinal fluid. This association may point to another cause for this condition[4]. There is also a patient case of delayed gemcitabine-induced PRES described in the literature by Schaub and Tang[5].

It is a well-known fact that malignant tumors can cause activation of endothelial cells, proliferation and neovascularization, all which lead to vascular cerebral dysregulation. We speculate, thusly, that PRES may be caused by paraneoplastic antibodies, tumors or even antitumor therapy, per se, in addition to the hypercalcemia postulated by Song et al[1]. In this regard, we suggest that clinicians addressing similar cases in the future should include screening for paraneoplastic syndrome and parathyroid hormone changes in their clinical investigations. Since treatment success and overall prognosis are related to the underlying etiology, solidifying our knowledge of such on a case-by-case basis will benefit this patient population overall.

FOOTNOTES

Author contributions: Kunić S and Ibrahimagić OĆ designed the commentary; Kunić S, Kojić B and Džananović Dž performed the data analysis and wrote the letter; and Ibrahimagić OĆ revised the letter for important intellectual content

Conflict-of-interest statement: The authors declare no conflicts of interest.

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REFERENCES

1 Song CH, Lee SJ, Jeon HR. Posterior reversible encephalopathy syndrome in a patient with metastatic breast cancer: A case
Kunić S et al. Comment: PRES in metastatic breast cancer


