### Thrice Monthly Volume 9 Number 34 December 6, 2021

#### Contents

##### OPINION REVIEW

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10392</td>
<td>Regulating monocyte infiltration and differentiation: Providing new therapies for colorectal cancer patients with COVID-19</td>
<td>Bai L, Yang W, Qian L, Cui JW</td>
</tr>
</tbody>
</table>

##### REVIEW

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10400</td>
<td>Role of circular RNAs in gastrointestinal tumors and drug resistance</td>
<td>Xi SJ, Cai WQ, Wang QQ, Peng XC</td>
</tr>
</tbody>
</table>

##### MINIREVIEWS

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10418</td>
<td>Liver injury associated with acute pancreatitis: The current status of clinical evaluation and involved mechanisms</td>
<td>Liu W, Du JJ, Li ZH, Zhang XY, Zuo HD</td>
</tr>
<tr>
<td>10438</td>
<td>Role of immune escape in different digestive tumours</td>
<td>Du XZ, Wen B, Liu L, Wei YT, Zhao K</td>
</tr>
</tbody>
</table>

##### ORIGINAL ARTICLE

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10451</td>
<td>Magnolol protects against acute gastrointestinal injury in sepsis by down-regulating regulated on activation, normal T-cell expressed and secreted</td>
<td>Mao SH, Feng DD, Wang X, Zhi YH, Lei S, Xing X, Jiang RL, Wu JN</td>
</tr>
</tbody>
</table>

#### Case Control Study

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10464</td>
<td>Effect of Nephritis Rehabilitation Tablets combined with tacrolimus in treatment of idiopathic membranous nephropathy</td>
<td>Lv W, Wang MR, Zhang CZ, Sun XX, Yan ZZ, Hu XM, Wang TT</td>
</tr>
</tbody>
</table>

#### Retrospective Cohort Study

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10484</td>
<td>Clinical features and survival of patients with multiple primary malignancies</td>
<td>Wang XK, Zhou MH</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>10494</td>
<td>Thoracoscopic segmentectomy and lobectomy assisted by three-dimensional computed-tomography bronchography and angiography for the treatment of primary lung cancer</td>
<td>Wu YJ, Shi QT, Zhang Y, Wang YL</td>
</tr>
<tr>
<td>10507</td>
<td>Endoscopic ultrasound fine needle aspiration vs fine needle biopsy in solid lesions: A multi-center analysis</td>
<td>Moura DTH, McCarty TR, Jirapinyo P, Ribeiro IB, Farias GFA, Madruga-Neto AC, Ryou M, Thompson CC</td>
</tr>
<tr>
<td>10518</td>
<td>Resection of bilateral occipital lobe lesions during a single operation as a treatment for bilateral occipital lobe epilepsy</td>
<td>Lyu YE, Xu XF, Dai S, Feng M, Shen SP, Zhang GZ, Ju HY, Wang Y, Dong XB, Xu B</td>
</tr>
<tr>
<td>10530</td>
<td>Improving rehabilitation and quality of life after percutaneous transhepatic cholangiography drainage with a rapid rehabilitation model</td>
<td>Xia LL, Su T, Li Y, Mao JF, Zhang QH, Liu YY</td>
</tr>
<tr>
<td>10540</td>
<td>Combined lumbar muscle block and perioperative comprehensive patient-controlled intravenous analgesia with butorphanol in gynecological endoscopic surgery</td>
<td>Zhu RY, Xiang SQ, Chen DR</td>
</tr>
<tr>
<td>10549</td>
<td>Teicoplanin combined with conventional vancomycin therapy for the treatment of pulmonary methicillin-resistant <em>Staphylococcus aureus</em> and <em>Staphylococcus epidermidis</em> infections</td>
<td>Wu W, Liu M, Geng JJ, Wang M</td>
</tr>
<tr>
<td>10566</td>
<td>Comparative study for predictability of type 1 gastric variceal rebleeding after endoscopic variceal ligation: High-frequency intraluminal ultrasound study</td>
<td>Kim JH, Choe WH, Lee SY, Kwon SY, Sung IK, Park HS</td>
</tr>
<tr>
<td>10576</td>
<td>Effects of WeChat platform-based health management on health and self-management effectiveness of patients with severe chronic heart failure</td>
<td>Wang ZR, Zhou JW, Liu XP, Cai GJ, Zhang QH, Mao JF</td>
</tr>
<tr>
<td>10585</td>
<td>Early cardiopulmonary resuscitation on serum levels of myeloperoxidase, soluble ST2, and hypersensitive C-reactive protein in acute myocardial infarction patients</td>
<td>Hou M, Ren YP, Wang R, Lu LX</td>
</tr>
<tr>
<td>10595</td>
<td>Remimazolam benzenesulfonate anesthesia effectiveness in cardiac surgery patients under general anesthesia</td>
<td>Tang F, Yi JM, Gong HY, Lu ZY, Chen J, Fang B, Chen C, Liu ZY</td>
</tr>
</tbody>
</table>
## Contents

**Randomized Clinical Trial**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10604</td>
<td>Effects of lower body positive pressure treadmill on functional improvement in knee osteoarthritis: A randomized clinical trial study</td>
<td>Chen HX, Zhan YX, Ou HN, You YY, Li WY, Jiang SS, Zheng MF, Zhang LZ, Chen K, Chen QX</td>
</tr>
</tbody>
</table>

**SYSTEMATIC REVIEWS**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10616</td>
<td>Effects of hypoxia on bone metabolism and anemia in patients with chronic kidney disease</td>
<td>Kan C, Lu X, Zhang R</td>
</tr>
</tbody>
</table>

**META-ANALYSIS**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10626</td>
<td>Intracuff alkalinized lidocaine to prevent postoperative airway complications: A meta-analysis</td>
<td>Chen ZX, Shi Z, Wang B, Zhang Y</td>
</tr>
</tbody>
</table>

**CASE REPORT**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10645</td>
<td>Diagnosis, fetal risk and treatment of pemphigoid gestationis in pregnancy: A case report</td>
<td>Jiao HN, Ruan YP, Liu Y, Pan M, Zhong HP</td>
</tr>
<tr>
<td>10652</td>
<td>Histology transformation-mediated pathological atypism in small-cell lung cancer within the presence of chemotherapy: A case report</td>
<td>Ju Q, Wu YT, Zhang Y, Yang WH, Zhao CL, Zhang J</td>
</tr>
<tr>
<td>10666</td>
<td>Excimer laser coronary atherectomy for a severe calcified coronary ostium lesion: A case report</td>
<td>Hou FJ, Ma XT, Zhou YJ, Guan J</td>
</tr>
<tr>
<td>10681</td>
<td>Intravascular papillary endothelial hyperplasia as a rare cause of cervicothoracic spinal cord compression: A case report</td>
<td>Gu HL, Zheng XQ, Zhan SQ, Chang YB</td>
</tr>
<tr>
<td>10689</td>
<td>Proximal true lumen collapse in a chronic type B aortic dissection patient: A case report</td>
<td>Zhang L, Guan WK, Wu HP, Li X, Lv KP, Zeng CL, Song HH, Ye QL</td>
</tr>
<tr>
<td>10696</td>
<td>Tigecycline sclerotherapy for recurrent pseudotumor in aseptic lymphocyte-dominant vasculitis-associated lesion after metal-on-metal total hip arthroplasty: A case report</td>
<td>Lin IH, Tsai CH</td>
</tr>
</tbody>
</table>
# Contents

**Thrice Monthly Volume 9 Number 34 December 6, 2021**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10702</td>
<td>Acute myocardial infarction induced by eosinophilic granulomatosis with polyangiitis: A case report</td>
<td>Jiang XD, Guo S, Zhang WM</td>
</tr>
<tr>
<td>10708</td>
<td>Aggressive natural killer cell leukemia with skin manifestation associated with hemophagocytic lymphohistiocytosis: A case report</td>
<td>Peng XH, Zhang LS, Li LJ, Guo XJ, Liu Y</td>
</tr>
<tr>
<td>10715</td>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma complicated with skin Langerhans cell sarcoma: A case report</td>
<td>Li SY, Wang Y, Wang LH</td>
</tr>
<tr>
<td>10723</td>
<td>Severe mediastinitis and pericarditis after endobronchial ultrasound-guided transbronchial needle aspiration: A case report</td>
<td>Koh JS, Kim YJ, Kang DH, Lee JE, Lee SI</td>
</tr>
<tr>
<td>10728</td>
<td>Obturator hernia - a rare etiology of lateral thigh pain: A case report</td>
<td>Kim JY, Chang MC</td>
</tr>
<tr>
<td>10733</td>
<td>Tracheal tube misplacement in the thoracic cavity: A case report</td>
<td>Li KX, Luo YT, Zhou L, Huang JP, Liang P</td>
</tr>
<tr>
<td>10738</td>
<td>Peri-implant keratinized gingiva augmentation using xenogeneic collagen matrix and platelet-rich fibrin: A case report</td>
<td>Han CY, Wang DZ, Bai JF, Zhao LL, Song WZ</td>
</tr>
</tbody>
</table>
ABOUT COVER
Editorial Board Member of *World Journal of Clinical Cases*, Gagan Mathur, MBBS, MD, Associate Professor, Director, Staff Physician, Department of Pathology, Saint Luke's Health System, Kansas City, MO 64112, United States. gmathur@saint-lukes.org

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 indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self-cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*’s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Yan-Xia Xing; Production Department Director: Yu-Jie Ma; Editorial Office Director: Jin-Lei Wang.
Regulating monocyte infiltration and differentiation: Providing new therapies for colorectal cancer patients with COVID-19

Ling Bai, Wang Yang, Lei Qian, Jiu-Wei Cui

Abstract

The outbreak of coronavirus disease 2019 (COVID-19) is a significant challenge for clinicians, especially for immunocompromised cancer patients. By analyzing the impact of COVID-19 on the immune microenvironment of colorectal cancer (CRC) patients at the tissue level and single-cell level, we found that CRC patients are more easily infected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), but promotion of infiltration and differentiation of monocytes makes them more likely to develop severe COVID-19. Because of the continuing activation of nuclear factor (NF)-κB and C-C chemokine receptor type 5 (CCR5) signaling pathways in monocytes, imbalance of macrophage polarization can aggravate the cytokine release syndrome. Therefore, regulating the infiltration and differentiation of monocytes is helpful for the treatment of COVID-19 in CRC patients.

Key Words: COVID-19; SARS-CoV-2; Monocyte; Macrophage; Colorectal cancer

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Not only are colorectal cancer (CRC) patients susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) but their infiltrating monocytes are also affected by SARS-CoV-2. Promotion of infiltration and differentiation of monocytes after infection CRC patients are more likely to develop severe coronavirus disease 2019 (COVID-19). In severe COVID-19, because of activation of the nuclear factor (NF)-κB and C-C chemokine receptor type 5 (CCR5) signaling pathways, the imbalance of macrophage polarization can cause further aggravation of the cytokine release syndrome.

Citation: Bai L, Yang W, Qian L, Cui JW. Regulating monocyte infiltration and differentiation:
SARS-COV-2 RECOGNITION PROTEINS ARE HIGHLY EXPRESSED IN THE TUMOR TISSUES OF CRC PATIENTS

After SARS-CoV-2 infection, viral envelope spike proteins bind to ACE2 and promote cellular recognition of the virus[2]. If transmembrane serine protease 2 (TMPRSS2) is present, it promotes the cleavage and activation of S proteins by host cells. SARS-CoV-2 usually enters cells through the endosomal pathway, but in the absence of TMPRSS2, it enters by cathepsin L (CTSL) and cathepsin B (CTSB) proteolysis and activation of S protein[10-12].

Data on mRNA expression in colorectal cancer tissue in the Cancer Genome Atlas (https://cancergenome.nih.gov/) and the Genotype-Tissue Expression project (https://www.gtexportal.org/home/) databases, we found that the expression of ACE2 and TMPRSS2 was higher in CRC than in healthy tissue (Figure 1A). In addition, single-cell sequencing data from 27,414 cells from six CRC patients in the National Center for Biotechnology Information Gene Expression Omnibus (GEO) database (GSE144735), we found that ACE2, TMPRSS2, CTSL, and CTSB were primarily expressed in stromal and epithelial cells of CRC tissue (Figure 1B, C). Therefore, the susceptibility of CRC patients to COVID-19 may be associated with the high expression of SARS-CoV-2 recognition proteins.

INTRODUCTION

As a public health emergency of international concern, there are nearly 150 million coronavirus disease 2019 (COVID-19) cases worldwide. In particular, cancer patients are more vulnerable to virus infection because of their suppressed immune microenvironment. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters cells by recognizing angiotensin I converting enzyme 2 (ACE2), transmembrane serine protease 2 (TMPRSS2)[1], and other proteases, such as cathepsin B (CTSB) and cathepsin L (CTSL)[2], in the host cell. Clarifying the expression of those proteins unique to various human pathologies may be helpful in identifying susceptible populations.

Studies have shown that cancer patients not only have a 2.31 times higher risk of infection with SARS-CoV-2 than the general population[3] but also have a higher risk of developing severe COVID-19[3,4]. Compared with patients without cancer, those with cancer have a 3.56-fold increased risk of severe disease following COVID-19 infection[5]. However, the mechanism of the exacerbation of COVID-19 is not clear. Therefore, revealing the effects of COVID-19 infection on the human body may provide new ideas for preventing the deterioration of COVID-19 patients.

The leading cause of COVID-19 aggravation is multiorgan dysfunction caused by the cytokine release syndrome (CRS). By comparing the differences in proteomics and metabolomics of severe and nonsevere COVID-19 cases with healthy controls, it was found that the severe cases were associated with abnormal macrophage regulation[6,7]. The results of meta-analysis and bioinformatics analysis have shown that colorectal cancer (CRC) patients are more susceptible to SARS-CoV-2 than cancer patients with other tumors[8]. Studies have also shown that COVID-19 patients with CRC are more likely to have clinical characteristics with a poor COVID-19 prognosis than matched patients with COVID-19 but without cancer[9]. We used CRC as an example to elucidate the effect of SARS-CoV-2 on the cancer immune microenvironment, especially the impact on monocytes, with the goal of finding treatments to delay the progression of COVID-19.

SARS-CoV-2 RECOGNITION PROTEINS ARE HIGHLY EXPRESSED IN THE TUMOR TISSUES OF CRC PATIENTS

URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10392.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10392
INFLAMMATORY MONOCYTES IN COLORECTAL CANCER TISSUES ARE SENSITIVE TO SARS-COV-2 INFECTION

Analysis of GEO single-cell sequencing data (GSE144735) revealed that expression of the CTSL and CTSB SARS-CoV-2 recognition proteins was higher in monocytes compared with other immune cells in the tumor microenvironment (Figure 2). Consequently, SARS-CoV-2 infection may affect the function of monocytes. The analysis also showed that the expression of CTSL and CTSB mRNA was higher in infiltrated monocytes in cells from tumor than it was in cells from healthy tissue (Figure 2). Thus, when infected by COVID-19, monocytes in the tumor microenvironment may induce a stronger inflammatory effect.

COVID-19 PROMOTES INFILTRATION AND DIFFERENTIATION OF MONOCYTES

Monocytes constitute a pool of dendritic cells and macrophages, and differentiate into type 1 macrophages (M1) and type 2 macrophages (M2). M1 are proinflammatory macrophages and have an anti-tumor effect. M2 are anti-inflammatory macrophages that mediate tumor immune escape. The effects of monocyte cytokines produced following SARS-CoV-2 infection on macrophage polarization was investigated using...
Figure 2 Infiltrating monocytes in colorectal cancer tissues express high levels of severe acute respiratory syndrome coronavirus 2 recognition proteins. Analysis of single-cell sequencing of 27,414 cells in six colorectal cancer patients identified genes that were expressed in at least three cells and at least 200 genes were identified in each cell. Harmony was used to remove batch effects. The first 20 principal components were selected in Seurat to cluster the patients, and the enriched pathways in marker gene sets were found with enrichr (https://amp.pharm.mssm.edu/Enrichr) and the expression of coronavirus disease 2019-related genes in dendritic, natural killer, myeloid, stromal, and epithelial cells; monocytes, and B cells was screened. Severe acute respiratory syndrome coronavirus 2 recognition proteins were mainly expressed on monocytes. The expression of angiotensin I converting enzyme 2, transmembrane serine protease 2, cathepsin B, and cathepsin L in tissue-infiltrated monocytes was higher in colorectal cancer than in normal tissue. ACE2: Angiotensin I converting enzyme 2; CRC: Colorectal cancer; CTSB: Cathepsin B; CTCL: Cathepsin L; TMPRSS2: Transmembrane serine protease 2; UMAP: Uniform manifold approximation and projection.

GEO data (GSE145926). Cluster-based processing of cells from three healthy, three mild, and six severe COVID-19 patient using Harmony (https://www.harmony-alliance.eu/covid19/covid-19-news/open-call-for-data-partners-to-join-the-harmony-covid-19-data-platform) was used to remove batch effects and select 20 principal components. Differential expression analysis with Seurat (https://satijalab.org/seurat//archive/v3.2/de_vignette.html) identified CD14+ monocytes in the patient samples for subsequent analysis. The proportions of M1 and M2 in the samples were determined by counting the CD80- and CD86-positive M1 and MRC1- and CD163-positive M2 cells. Differences were compared with GraphPad Prism 7.0a for Mac OS X (GraphPad Inc., La Jolla, CA, United States) and the unpaired two-tailed Student’s t-test. Numeric data are reported as means ± SD. The gene set variation analysis (GSVA) for microarray and RNA-seq data (https://www.bioconductor.org/packages/release/bioc/html/GSVA.html) R statistics package was used to score gene set enrichment analysis data from 31,557 monocytes (c2.cp.v7.1.symbols.gmt: https://data.broadinstitute.org/gsea-msigdb/msigdb/release/7.1/).

Analysis of the cytokines expressed by monocytes in alveolar lavage fluid (GEO: GSE145926, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE145926) showed that COVID-19 induced the differentiation of M1 and M2 by affecting the cytokines TGF-β1 and TNF-α (Figure 3A). Therefore, SARS-CoV-2 promotes macrophage polarization and enhances macrophage infiltration by stimulating...
cytokine production. By comparing the correlation between the proportion of macrophages and the degree of infection, it was found that patients with COVID-19 had higher macrophage infiltration than healthy people (Figure 3B). However, after developing into severe COVID-19, the M1/M2 ratio increased (Figure 3B), which may further aggravate the CRS.

**REGULATION OF MONOCYTE INFILTRATION AND DIFFERENTIATION MAY CONTRIBUTE TO THE TREATMENT OF COVID-19**

We use the Linear Models for Microarray (limma) R package (https://bioconductor.org/packages/release/bioc/html/limma.html) to distinguish signaling pathways (DEGenesets) in patients with severe and nonsevere COVID-19 infection and healthy controls and cutoffs of the average absolute between-group differences. We identified nine signaling pathways that were statistically different ($\geq 0.35$ false discovery rate-adjusted $P < 0.001$, Figure 4). The results suggest that COVID-19 infection promotes the activation of NF-κB and CCR5 signaling pathways in monocytes. Multiple metabolic pathways in monocytes are involved (Figure 4). Inhibiting the activation of the NF-κB or CCR5 signaling pathway is expected to maintain the balance of M1 and M2 monocytes and thus prevent progression to severe COVID-19 infection.

**CONCLUSION**

COVID-19 has many implications for the diagnosis and treatment of cancer. With the increasing understanding of the SARS-CoV-2 infection-related signaling pathway, a growing number of studies have described the association between tumors and the risk of COVID-19 infection. Clinical studies and meta-analyses have also preliminarily confirmed the susceptibility of Chinese CRC patients to COVID-19[13,14], but reason needs further study. This study briefly described the expression of SARS-CoV-2 recognition proteins in the cells and tissues of COVID-19 patients, providing a
Figure 4 Coronavirus disease 2019 infection promotes the activation of NF-κB and CCR5 signaling pathways in monocytes. The limma R package was used to identify differentially expressed pathways (DEGeneset) in severe and nonsevere Coronavirus disease 2019 (COVID-19) patients, and healthy controls with an absolute value score > 0.35 and a false discovery rate < 0.001. Nine differential pathways were found. COVID-19 infection promoted the activation of NF-κB and CCR5 signaling pathways in monocytes. Multiple metabolic pathways were also involved.

reference for subsequent studies on the susceptibility of CRC patients to COVID-19.

Because SARS-CoV-2 recognition proteins are not only expressed in tumor cells but also immune cells, we analyzed the expression of essential proteins related to COVID-19 infection in various immune cells by the single-cell sequencing analysis of cells in CRC patients. We found that SARS-CoV-2 infection may affect the function of monocytes and that SARS-CoV-2 infection can promote the activation of NF-κB and CCR5 signaling pathways in monocytes. Suppressing the activation of NF-κB and CCR5 signaling pathways may reshape the balance of macrophage polarization, which can be helpful for the treatment of COVID-19.

Because of the relationship between monocyte-macrophage activation and the severity of COVID-19, the cytokines released by epithelial cells and fibroblasts following SARS-CoV-2 infection promote the recruitment of monocytes and the activation of macrophages, which promotes the CRS[15]. We also uncovered evidence that monocyte-macrophage infiltration was associated with COVID-19 severity and that M1/M2 ratio was higher in severe than in nonsevere COVID-19, which promotes disease progression. We believe that the high expression of SARS-CoV-2 recognition protein in monocytes affects monocytes function in direct or indirect ways.

Statins are inhibitors of cholesterol synthesis. They are also helpful in the treatment of COVID-19[16], although it is not clear how they do that. Statins can not only directly inhibit the growth and development of tumors, but also inhibit the release of pro-differentiation cytokines by M1 macrophages. They also cause a reduction of the M1/M2 ratio and inhibit macrophage infiltration by inhibiting TLR4/MYD88/NF-κB signaling[17,18]. Furthermore, lipids promote the upregulation of CCR5 in monocytes and enhance their proinflammatory phenotype[19]. Inhibitors of NF-κB and CCR5, such as statins, may offer a novel treatment for CRC patients with COVID-19 by regulating the changes in the M1/M2 ratio. Because lipopolysaccharides are a TLR4 agonist, active prevention and treatment of combined bacterial infections may be effective to prevent CRS occurrence. Leronlimab, a CCR5-specific antibody, has also been reported as a potential treatment of COVID-19. It inhibits macrophage polarization and CRS occurrence by blocking CCR5[20,21]. We believe that other drugs that block NF-κB or CCR5 may also be effective in treating COVID-19.
REFERENCES


Role of circular RNAs in gastrointestinal tumors and drug resistance

Shi-Jun Xi, Wen-Qi Cai, Qin-Qi Wang, Xiao-Chun Peng

ORCID number: Shi-Jun Xi 0000-0003-2434-7722; Wen-Qi Cai 0000-0003-3901-4576; Qin-Qi Wang 0000-0003-1090-3812; Xiao-Chun Peng 0000-0001-9443-0439.

Author contributions: Peng XC designed and supervised the study; Xi SJ reviewed the references; Xi SJ and Peng XC wrote the manuscript; Xi SJ, Cai WQ and Wang QQ contributed to tables and figures.

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

Supported by: Natural Science Foundation of Hubei Province, China, No. 2017CFB786; Hubei Province Health and Family Planning Scientific Research Project, China, No. WJ2016Y10; Jingzhou Science and Technology Bureau Project, China, No. 2017-93; the College Students Innovative Entrepreneurial Training Program in Yangtze University, China, No. 2019376; and Postgraduate Innovation Fund Project of Yangtze University, China, No. 200202.

Country/Territory of origin: China

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report’s scientific

Abstract

The incidence of gastrointestinal cancers has increased significantly over the past decade and gastrointestinal malignancies now rank among the leading causes of mortality globally. Although newer therapeutic strategies such as targeted therapies have greatly improved patient outcomes, their clinical success is limited by drug resistance, treatment failure and recurrence of metastatic disease. Therefore, there is an urgent need for further research identifying accurate and reliable biomarkers for precise treatment strategies. Circular RNAs (circRNAs) exhibit a covalently closed structure, high stability and biological conservation, and their expression is associated with the occurrence and development of gastrointestinal tumors. Moreover, circRNAs may significantly influence drug resistance of gastrointestinal cancers. In this article, we review the role of circRNAs in the occurrence and development of gastrointestinal cancer, their association with drug resistance, and potential application for early diagnosis, treatment and prognosis in gastrointestinal malignancies. Furthermore, we summarize characteristics of circRNA, including mechanism of formation and biological effects via mRNA sponging, chromatin replication, gene regulation, translational modification, signal transduction, and damage repair. Finally, we discuss whether circRNA-related noninvasive testing may be clinically provided in the future. This review provides new insights for the future development of diagnostics and therapeutics based on circRNAs in gastrointestinal tumors.

Key Words: Gastrointestinal cancer; Circular RNA; Drug resistance; Genomics; Targeted therapy; Molecular mechanics

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Circular RNAs (circRNAs) were first discovered in 1976, and then more related biological functions were discovered. For example, as a miRNA sponging,
CircRNAs have complex biological functions in gastrointestinal tumors. Here, we discuss the sponging effect of circRNAs in tumors as well as their effects on chromatin modification, translation modification, and DNA damage repair. Gastrointestinal tumors have a high incidence, and some patients also show drug resistance during treatment. On this basis, we reviewed the relationship between circRNA and gastrointestinal tumors and the relevance of drug resistance, hoping to conduct more in-depth research on circRNA. At the same time, it is hoped that circRNA will provide new directions and strategies for future cancer treatment.

INTRODUCTION

The incidence of gastrointestinal tumors has increased significantly in recent years[1]. Gastrointestinal tumors, one of the most common cancer types, are increasingly treated with novel treatment strategies including targeted therapies and immunotherapies[2]. In clinical practice, pemetrexed, paclitaxel, cisplatin, sorafenib, and 5-fluorouracil (5-FU), among other drugs, are commonly used therapeutics, but the frequent emergence of drug resistance renders treatment extremely challenging. Radiotherapy and chemotherapy resistance are typically caused by both tumor-cell intrinsic and extrinsic mechanisms, including epithelial-mesenchymal transition (EMT), alterations in tumor microenvironment, and hypoxia signaling[3].

Circular RNAs (circRNAs) have been found to be associated with the occurrence and development of a variety of cancers. They were first detected in 1976 in both RNA viruses and eukaryotic cells[4], but were considered meaningless and an erroneous splicing structure at the time[5]. However, in 1993, Capel et al[6] found that circRNAs accounted for > 90% of adult testicular SRY transcription. In 2012, Salzman et al[7] reported circRNA transcription of hundreds of human genes. Work by Memczak et al[8] in 2013 revealed that circRNA exhibit regulatory effects, and later work demonstrated that circRNAs can represent competitive endogenous RNAs[9] (Figure 1). These preliminary studies laid the foundation for the later discovery that circRNA is involved in gastrointestinal tumors. Here, we highlight the relationship between circRNAs and the occurrence and development of gastrointestinal tumors, as well as drug resistance in these tumors.

Figure 1 highlights the timeline of breakthrough research on circRNAs and their potential application in the field of oncology.

INTRODUCTION TO circRNAs

circRNAs are circular RNA molecules formed by covalent sealing of single-stranded RNA molecules. The majority of circRNAs is located in the cytoplasm, circRNAs are highly stable and biologically conserved[10]. They have an uncapped 5' end and no polyA structure at the 3' end[11]. circRNAs usually occur during the splicing process after transcription[12], and the majority of circRNAs can be degraded by RNase L endonuclease while they cannot be easily degraded by exonuclease[13]. circRNAs are considered functional noncoding transcripts that can produce functional peptides or proteins[14]: studies have shown that many circRNAs are translated and therefore circRNAs cannot be defined as entirely noncoding RNAs. For example, the 220-nucleotide CCC RNA in the wheat germ extraction system provided the first proof of natural circRNA translation in 2014[15]. Moreover, some circRNAs have an N6-
methyladenosine (m6A) modification that promotes the translation of circRNAs and plays a role in either inhibition or promotion of tumor progression[16,17]. circRNAs are suggested to be involved in the progression and drug resistance of a variety of cancers, although further studies need to be conducted to confirm the exact mechanisms of action[18]. By understanding the properties and functions of circRNAs, we can further explore the mechanisms of their involvement in gastrointestinal tumors as well as potential future applications for diagnosis and treatment.

Mechanisms of circRNA formation

In recent years, there have been several studies investigating the formation of circRNAs. circRNAs are divided into four types: exonic, intronic, exon-intron, and intergenic[19]. At present, the mechanisms of circRNA processing and maturation are still largely unclear[20], but recent studies suggest that 80% of circRNAs are exonic circRNAs (ecircRNA), which have two key formation mechanisms: lasso-driven circularization (exon skipping) and intron pair-driven circularization (direct reverse splicing)[21] (Figure 2). mRNA intron lassos can evade degradation during splicing, forming circRNA with 2', 5’phosphodiester bonds, and the same sequence can form different circRNAs via different types of splicing. Not all exons can be spliced to form circRNAs, however the more spliced an RNA is, the less fully processed mRNA exists, for example in the rat P4502C24 gene[22].

There are also other theories that state that circRNAs can be formed by RNA-binding proteins (RBPs) or flanking introns that interact with each intron through RNA–RNA interaction to promote the combination of both ends of the head and tail, ultimately leading to the formation of intronic circRNAs (ciRNAs) or exon-intron circRNAs (EiCiRNAs). More research investigating the formation mechanisms of circRNA in-depth will thus be required in the future.

Biological function of circRNAs

circRNA sponge effects: circRNAs are associated with various conditions and diseases including aging, defect insulin secretion, Alzheimer’s disease, gastrointestinal tumors, as well as cardiovascular and cerebrovascular diseases, to name a few[23-26]. Generally, circRNAs bind to mRNAs by base complementary pairing, thereby potentially participating in the tumor related processes[27].

CDR1as is the product of cerebellar degeneration-related protein 1 (CDR1), also known as ciRS-7[28]. Knockdown of CDR1as can promote the degradation of miR-7-targeted mRNA and can act as a miR-7 sponge[29,30]. It has been reported that in addition to ciRS-7, circPVT1 may also promote cell proliferation by acting as a sponge for miR-125 family members[31]. circRNAs can also act as sponges for RBPs or miR-138 family members[32,33].

circRNAs exhibit a sponging activity for specific miRNAs, thereby inhibiting miRNA-based inhibition of gene expression.

Impact of circRNAs on chromatin replication: Increasing numbers of studies have shown that circRNAs are involved in chromatin replication. Chromatin replication includes DNA and nucleosome replication, during which nucleosomes interact with nucleoproteins that are important for protein recruitment, DNA replication, transcription, and damage repair[34]. DNA replication occurs in the nucleus[35]. During chromatin replication, certain proteins may be recruited which help to
organize chromatin regions and regulate gene expression. Chromatin immunoprecipitation (ChIP) sequencing technology has detected the presence of nuclear circRNAs during chromatin replication, which indicates that circRNAs may play a role in this process\cite{36}. Moreover, ChIP studies have also found that overexpression of circRNAs inhibits tumor proliferation in bladder cancer\cite{37}. Clarifying the role of circRNAs in chromatin replication may therefore provide future insights for inhibiting tumor proliferation.

**CircRNA regulation of gene transcription:** circRNAs regulate gene transcription function and play an important role in gastrointestinal tumors. Studies have shown that addition of m6A is a reversible transcriptomic modification found in many eukaryotic mRNAs\cite{38}. m6A modification of circRNAs aids their translation to proteins\cite{39,40}. For example, circ-FBXW7 can be translated into the FBXW7-185aa protein after m6A modification\cite{14}. Circular structures may even be translated into more proteins than linear structure in the ribosome\cite{41}. circRNAs are transcribed by RNA polymerase (Pol) II and can be produced by spliceosomes, including heterogeneous nuclear ribonucleoproteins (hnRNPs)\cite{42}. For example, when precipitating circEIF3J or circPAIP2, PolII, U1A, U1c and U1 small nuclear RNAs are detected. Similarly, ElcRNAs can interact with Pol II, U1 hnRNP and parental gene promoters to enhance the transcription of parent genes, thus affecting protein translation\cite{43}. The peptides encoded by circRNA can interfere with the metabolism or metastasis of tumors, thereby exerting an antitumor effect\cite{44}. Nuclear circRNAs act as transcriptional or splicing regulators that interfere with gene expression and participate in selective splicing and transcription processes\cite{45}. For instance, circITGA7 plays a negative regulatory role in the Ras pathway and inhibits RREB1 upregulation through the Ras pathway, which typically results in ITGA7 transcription\cite{46}. circSHKBP1 has been shown to act as a miR-582-3p sponge and regulates the HUR/VEGF pathway in the promotion of the progression of gastric cancer\cite{47}.

To summarize, circRNAs play many biological roles and are involved in splicing, transcriptional or translational regulation, sequestering of miRNA, and protein binding. Although the mechanisms are largely unclear, circRNAs are likely to play a vital role in tumor development via these processes.

**circRNA post-translational modifications (PTMs):** Modifications can be regulated by the structure of chromatin, and it can also use ATP hydrolysis to generate energy to relocate the recombinase, and post-translational histone modifications, such as acetylation, phosphorylation, methylation and many other forms\cite{48}. PTMs often
circRNAs and signal transduction: Signal transduction pathways often undergo abnormal changes in the occurrence and development of tumors. In osteosarcoma, circTCF25 has been shown to promote phosphorylation of signal transducers and produce carcinogenic effects[53]. In lung cancer, circ-ZKSCAN1/miR-330-5p/FAM83A can regulate the signal transduction pathway, and the reduction of circ_ZKSCAN1 can inhibit tumor cell migration and proliferation[54]. In breast cancer, hsa-circ-0061825 (circ-TFF1) may promote progression by affecting miR-326/TFF1 signaling[55]. circFMN2 may promote colorectal cancer progression via the miR-1182/hTERT signaling pathway[56]. circ0000190 has been shown to inhibit proliferation and metastasis of gastric cancer cells by regulation of caspase-3 expression and inhibition of the miR-1252/PAK3 pathway[57]. Exploring diverse signaling pathways influenced by circRNA may provide potential therapeutic targets relating to tumor development and progression in the future.

circRNAs and damage repair: DNA breaks are characterized as single- or double-strand[58]. In vivo repair mechanisms support the precise repair of single-strand breaks, while double-strand breaks often lead to cell death[59]. The occurrence of tumors is sometimes related to radiation, which causes DNA double-strand breaks. In noncoding RNA, the signal ionizing radiation response can be adjusted by targeting [60]. In breast cancer, circSMARCA5 can participate in the remodeling of damaged chromatin DNA[61]. Assessing the influence of circRNAs on DNA damage repair mechanisms in different cells may provide valuable information for DNA repair in the future.

circRNAs AS BIOMARKERS AND THERAPEUTIC TARGETS IN GASTROINTESTINAL TUMORS

Tumor development is a complicated pathological process. Molecules such as noncoding RNAs and cell-free DNA may be used as potential biomarkers but also therapeutic targets for benign and malignant diseases of the gastrointestinal tract[62]. The mechanism of anticancer drug resistance is multifaceted. Tumor growth, tumor microenvironment, immune system, and selective treatment pressure all affect tumor resistance[63]. Unfortunately, some patients develop drug resistance that requires exploration of other treatment directions. Therefore, drug resistance research is a key area of investigation. Several studies have suggested that circRNAs may play a key role not only as therapeutic targets for digestive system tumors but targeting them may also help to overcome drug resistance.

circRNAs regulate gastric cancer progression and drug resistance

Owing to their special circular structure, circRNAs can be stably present in peripheral bodily fluids such as saliva and plasma, and can remain stable in serum for >24 h[64]. Research has found that out of 11 circRNAs assessed, five were upregulated and promoted cancer, while six were downregulated and exhibited cancer-suppressing effects[65].

circRNA100876 is highly expressed in gastric cancer (GC) tissues and influences the miR-665/YAP1 signaling pathway. It can inhibit the proliferation, invasion and migration of GC cells by downregulation of the EMT pathway[66]. Conversely, studies have shown that circCUL3 can promote extracellular acidification rate, lactic acid production, and GC cell proliferation. This circRNA is highly expressed in GC tumor cells and has been shown to promote the expression of signal transducer and activator of transcription (STAT) pathways.
of transcription (STAT) 3 via sponging of mir-515-5p[67]. Similarly, circTMEM87A is also highly expressed in GC and can sponge mir-142-5p, regulating ULK1 expression and thus promoting GC proliferation and metastasis[68]. circRNA-0044516 is likewise upregulated in GC and acts as a mir-149 sponge. circRNA-0044516 silencing results in reduced Wnt1 and β-catenin protein levels and inhibits GC progression[69]. circ0000039 is also upregulated in GC, adsorbs mir-1292-5p, and upregulates DEK expression to promote GC proliferation and progression as an oncogene[70]. Circ-0004872 is significantly downregulated in GC tumor cells and has a tumor-suppressive effect. It acts as a mir-224 sponge and upregulates expression of mir-224 downstream targets p21 and Smad4[71]. circ-ITCH is also lowly expressed in GC. It negatively regulates the Wnt/β-catenin signaling pathway as a tumor suppressor, inhibiting tumor occurrence and development[72]. circPpizD8 is an oncogene circRNA that is upregulated in GC tissues and cells and acts as a miR-197-5p sponge. Its knockout is beneficial for suppression of tumor occurrence[73].

circRNAs participate in various pathological processes. However, their participation in processes such as drug resistance is not mediated by simple up- or downregulation. Their special covalent closed-loop structures play biological roles in transcription and translation, and these mechanisms need to be further explored and characterized. Studies have shown that circMTHFD2 can promote GC cell resistance to pemetrexed via molecular sponging of mir-124, thereby increasing the patient’s medication time for pemetrexed, reducing the occurrence of drug resistance, and prolonging patient survival[74]. circPVT1 enhances the sensitivity of GC cells to paclitaxel by negatively regulating mir-124-5p, and its knockdown increases the sensitivity of gastric cancer to paclitaxel[75]. circAKT3 promotes DNA damage repair both in vivo and in vitro and inhibits apoptosis in GC patients. Moreover, circAKT3 promotes PI3K/R expression via miR-198 targeting, and circAKT3 downregulation, which is conducive to the cisplatin sensitivity of GC cells, indicating that circAKT3 knockdown inhibits further growth of GC, improves GC sensitivity and prolongs survival of patients using cisplatin drugs[76]. circFN1 (hsa-circ-0058147) is predominantly located in the cytoplasm and regulates cisplatin activity via mir-182-5p targeting, preventing the ability of mir-182-5p to activate caspase-3 via phosphorylation and inhibition of apoptosis in GC patients. Several studies point towards an involvement of circFN1 in cisplatin resistance and it may represent a future therapeutic target for cisplatin resistance in patients with GC[77]. circRNA may play a role in GC through regulating signaling pathways, and have an impact on the development of drug resistance in these GC patients. The specific mechanisms need to be further studied, but given the evidence so far, the role of circRNAs in GC should not be underestimated. Thus, circRNAs may play an important role as a potential diagnostic and prognostic indicators of GC in the future (Table 1).

circRNAs regulate liver cancer progression and drug resistance

Hepatocellular carcinoma (HCC) has become one of the leading global cancers with an extremely high fatality rate. The prevalence of liver cancer is higher in men than in women, and it is related to risk factors such as hepatitis B and C, smoking, diabetes, and Aspergillus infections[78]. Studies have demonstrated that several circRNAs may either be potential biomarkers for the diagnosis of HCC or represent therapeutic targets for inhibiting tumor development. For example, hsa-circ-0004018 is highly sensitive to α-fetoprotein and circ-0016788 may represent a personalized treatment for HCC patients[79]. Similarly, circZKSCAN1 and circPCNX may be used as diagnostic markers for liver cancer[80], while hsa-circRNA-100084 acts as a sponge for hsa-miR-23A-5P, promoting IGF2 expression[81]. circ-0051443 is transferred from normal cells to cancer cells via exosomes and exerts tumor-suppressing functions, inhibiting HCC[82]. circ-0091579 suppresses HCC proliferation and metastasis via targeting miRNA-490-3p. circABCB10 acts as a mir-670-3p sponge, upregulating HMG20A expression and thereby promoting HCC development. However, circABCB10 knockdown inhibits the migration and metastasis of tumor cells[83]. The mechanisms of action of circRNAs in liver cancer need to be further investigated to achieve better insights regarding their role and therapeutic potential.

Patients with liver cancer often face drug resistance. circRNAs have been found to influence drug resistance in several studies. For example, circRNA-101237 is associated with cisplatin sensitivity in HCC patients. Increased levels of circRNA101237 have been reported in the serum of cisplatin-resistant HCC patients and Huh7 cells, and patients with high expression typically have poor prognosis and low survival rates. circRNA_101237 can be used as an independent predictor of the prognosis of liver cancer patients[84]. hsa-circ-u0006294, hsa-circ-u0035944 and hsa-circ-u0084663 activate the Wnt/β-catenin pathway and inhibit HCC growth; of these, hsa-circ-
**Table 1** circRNAs involved in gastric cancer gene transcription regulation and drug resistance

<table>
<thead>
<tr>
<th>Cancer species</th>
<th>circRNA</th>
<th>Gene expression</th>
<th>Mechanism</th>
<th>Drug</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric cancer</td>
<td>circRNA108876</td>
<td>↑</td>
<td>Via miR-665/YAP1 signaling pathway</td>
<td>NR</td>
<td>[66]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>circCUL3</td>
<td>↑</td>
<td>Acts as a sponge for miR-515-5p</td>
<td>NR</td>
<td>[67]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>circTMEM87A</td>
<td>↑</td>
<td>Acts as a sponge for miR-142-5p</td>
<td>NR</td>
<td>[68]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>circRNA0044516</td>
<td>↑</td>
<td>Acts as a sponge for miR-149</td>
<td>NR</td>
<td>[69]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>circ0000309</td>
<td>↑</td>
<td>Acts as a sponge for miR-1292-5p</td>
<td>NR</td>
<td>[70]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>has-circ-0004872</td>
<td>↓</td>
<td>Acts as a sponge for miR-224</td>
<td>NR</td>
<td>[71]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>circ-ITCH</td>
<td>↓</td>
<td>Negative regulation of Wnt/β-catenin signaling pathway</td>
<td>NR</td>
<td>[72]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>circPDZD8</td>
<td>↑</td>
<td>Acts as a sponge for miR-197-5p</td>
<td>NR</td>
<td>[73]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>circMTHFD2</td>
<td>↑</td>
<td>Combined with miR-124 to exert sponge effect and induce MDR-1 protein</td>
<td>Pemetrexed</td>
<td>[74]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>circ-PVT1</td>
<td>↑</td>
<td>By negatively regulating miR-124-3p</td>
<td>Paclitaxel</td>
<td>[75]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>circAKT3</td>
<td>↑</td>
<td>Promote PIK3R1 expression through miR-198</td>
<td>Cisplatin</td>
<td>[76]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>circFlashsha-circ-0058147</td>
<td>↑</td>
<td>Regulation of cisplatin activity via miR-182-5p</td>
<td>Cisplatin</td>
<td>[77]</td>
</tr>
</tbody>
</table>

NR: Not reported; circRNA: Circular RNA.

u006294 and hsa-circ-u0035944 have been found to be downregulated in HCC and influence sorafenib resistance[85]. Likewise, circ-0003418, which inhibits the Wnt/β-catenin pathway, is downregulated in HCC, but increases the sensitivity of HCC to cisplatin. Conversely, knocking down circ-0003418 promotes HCC growth and proliferation[86], circFBXO11 is upregulated in HCC and promotes progression and oxaliplatin resistance via the miR-605/FOXO3/ABCB1 axis[87].

Liver resection and liver transplantation are common surgical treatments for patients with liver cancer[88]. Patients usually require radiotherapy and chemotherapy after surgical resection. However, with chemotherapy and targeted medication, drug resistance often occurs and the probability of liver cancer recurrence is high with poor prognosis. As presented in the results above, circRNAs have been shown to regulate HCC tumor growth, differentiation, apoptosis and migration. These and future studies may enable the application of circRNAs as potential prospective biomarkers in liver cancers, and the above-mentioned circRNAs may also have certain regulatory effects on drug resistance. Further in-depth research will likely provide new diagnostic indicators for liver cancer patients (Table 2).

**circRNAs regulate colorectal cancer progression and drug resistance**

Colorectal cancer (CRC) is the third most deadly and fourth most commonly diagnosed cancer in the world. Alcohol, tobacco, sedentary lifestyles and obesity have been reported to increase the risk of CRC[89]. It is estimated that by 2030, the global incidence of CRC will be as high as 60%, meaning that there will be nearly 1.4 million new patients[90]. Many circRNAs are dysregulated in CRC tissues compared with the normal mucosa. circNSUN2 is opposite to the 5p15 amplicon and interacts with YTHDC1, SRSF3, and NXF1. Upregulation of circNSUN2 in CRC promotes metastasis and is associated with poor prognosis; as a cancer-promoting circRNA, it may be used as a clinical diagnostic or prognostic marker in the future[91]. hsa-circ-101555 (circ101555) is also a cancer-promoting circRNA that sponges miR-597-5p, whose potential targets are CDK6 and RPA3. hsa-circ-101555 knockdown results in inhibition of CRC proliferation and metastasis, thus it may also be used as a future prognostic factor and therapeutic target for CRC[92]. High levels of circHIPK3 expression result in a low overall survival rate of CRC, and there is a negative correlation between circHIPK3 expression and CRC survival. circHIPK3 can inhibit the proliferation, migration and invasion of CRC cells[93]. circCCDC66 exerts its function by regulation of a subset of oncogenes, and studies have shown that circCCDC66 knockout inhibits CRC cell growth and invasion, while circCCDC66 upregulation results in poor CRC
Table 2 circRNAs involved in liver cancer gene transcription regulation and drug resistance

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>circRNA</th>
<th>Gene expression</th>
<th>Mechanism</th>
<th>Drug</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver cancer</td>
<td>circ10084</td>
<td>↑</td>
<td>Promotes IGF2 expression by acting as a sponge for HSA-MIR-23A-5P</td>
<td>NR</td>
<td>[81]</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>circABCB10</td>
<td>↑</td>
<td>Upregulates HMG20A expression by acting as a miR-670-3p sponge</td>
<td>NR</td>
<td>[83]</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>circRNA-101237</td>
<td>↑</td>
<td>Increased levels in serum and Huh7 cells of cisplatin-resistant HCC patients</td>
<td>Cisplatin</td>
<td>[84]</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Hsa-circ-u0006294, hsa-circ-u0035944, hsa-circ-u0084663</td>
<td>↓</td>
<td>Plays a role by activating the Wnt/β-catenin pathway</td>
<td>Sorafenib</td>
<td>[85]</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>circ-0003418</td>
<td>↓</td>
<td>Inhibits Wnt/β-catenin pathway</td>
<td>Cisplatin</td>
<td>[86]</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>circFBXO11</td>
<td>↑</td>
<td>Uses miR-605 /FOXO3/ABCB1 axis adjustment</td>
<td>Oxaliplatin</td>
<td>[87]</td>
</tr>
</tbody>
</table>

NR: Not reported; circRNA: Circular RNA.

Esophageal cancer (EC) is an extremely aggressive type of cancer with a 5-year survival rate between 15% and 20%. EC is the eighth most prevalent tumor in the world and the sixth leading cause of cancer-related deaths. Due to its poor prognosis and low survival rate, it is particularly important to identify the reliable biomarkers for its early diagnosis[105].

A study has reported 1045 upregulated and 1032 downregulated circRNAs in EC[106], and several studies have suggested that circRNAs play an important role in the regulation of gene transcription in EC. For example, hsa-circ-0004771 promotes esophageal squamous cell carcinoma via the miR-339-5P/CDC25A axis, and its knockdown inhibits proliferation and migration of development of esophageal squamous-cell carcinoma (ESCC). Nonetheless, its mechanisms of action have not been
Table 3 circRNAs involved in colon cancer gene transcription regulation and drug resistance

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>circRNA</th>
<th>Gene expression</th>
<th>Mechanism</th>
<th>Drug</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td>circNSUN2</td>
<td>↑</td>
<td>Interact with YTHDC1, SRSF3 and NXF1</td>
<td>NR</td>
<td>[91]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>has-circ-101555</td>
<td>↑</td>
<td>Acts as miR-597-5p sponge</td>
<td>NR</td>
<td>[92]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>circHIPK3</td>
<td>↑</td>
<td>Acts as miR-7 sponge</td>
<td>NR</td>
<td>[93]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>circCCDC66</td>
<td>↑</td>
<td>DDX9 phosphorylation</td>
<td>Oxaliplatin</td>
<td>[94,95]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>circ-001680</td>
<td>↑</td>
<td>Adjust BM1 via miR-340</td>
<td>Irinotecan</td>
<td>[98]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>has-circ-0005963</td>
<td>↑</td>
<td>Acts as miR-122 sponge</td>
<td>Oxaliplatin</td>
<td>[99]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>circ-0000338</td>
<td>↑ or ↓</td>
<td>Knock out circ-0000338 improves drug resistance</td>
<td>5-FU</td>
<td>[100]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>has-circ-32883</td>
<td>↑</td>
<td>uncertain</td>
<td>5-FU, oxaliplatin</td>
<td>[101]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>circ0007031, circ0000504, circ0007006</td>
<td>↑</td>
<td>Use has-miR485-5p pathway</td>
<td>5-FU</td>
<td>[102]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>has-circ-0079662</td>
<td>↑</td>
<td>Using the TNF-a pathway</td>
<td>oxaliplatin</td>
<td>[103]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>circDDX17</td>
<td>↑</td>
<td>Adjustable via miR-31-5p/KANK1 axis</td>
<td>5-FU</td>
<td>[104]</td>
</tr>
</tbody>
</table>

NR: Not reported; circRNA: Circular RNA.

fully elucidated[107]. circUBAP2 is upregulated in ESCC and acts as a miR-422a sponge. circUBAP2 knockdown inhibits ESCC progression and prevents the spread of tumor cells[108]. hasa-circ-0006948 is likewise upregulated in ESCC and promotes the growth and development of tumor cells via the miR-490-3p/HMGAA2 axis[109]. Similarly, circ-0000654 is upregulated in ESCC. It promotes proliferation and migration of tumor cells via the miR-149-5p/IL-6/STAT3 axis and tumor progression can be suppressed by circ-0000654 knockdown[110]. circGSK3 is another upregulated circRNA in ESCC. It promotes tumor cell proliferation via β-catenin signaling, which is positively correlated with poor prognosis[111]. circ-Foxo3 exhibits low expression in ESCC and modulates the miR-23a/PTEN pathway to inhibit ESCC development[112].

circPVT1 has been found to be significantly upregulated in EC and is suggested to play a role in the proliferation of TE-10 tumor cells via miR-4663[113].

ciRS-7 is abnormally increased in ESCC and promotes tumor cell growth. It may act as an oncogene, promoting promotes tumor cells proliferation by acting as a miR-876-5p sponge. Meng et al[114] have shown that ciRS-7 inhibits autophagy in ESCC induced by starvation or rapamycin immunosuppressive agents. Huang et al[115] confirmed that ciRS-7 promotes migration and invasion of ESCC cells via miR-7/KLF4 and NF-kB signaling pathways. Knockdown of KLF-4 in ESCC attenuates ciRS-7 invasion[114,115]. Drug resistance in EC is affected by cell proliferation, metastasis, glycolytic enzymes and other factors, among them circRNAs, IncRNAs, miRNAs, and acetyl-coenzyme, a synthetase short-chain family member 2 (ACSS2). Of the above-mentioned factors, IncRNAs have been particularly well studied. For example, ACSS2 affects the absorption of cisplatin in ESCC and protects cancer cells from cisplatin [116]. Conversely, research investigating the relationship between circRNAs and EC drug resistance is lacking. It has been demonstrated that circRNA-001275 upregulates Wnt family member 7A (Wnt7a), which triggers tumor cell growth via cisplatin, via miR-370-3p, inducing drug resistance[117]. Although there are few studies on circRNA in esophageal cancer drug resistance (Table 4), it can be expected that more circRNAs that play a role in the development and resistance of esophageal cancer will be discovered.

**circRNAs regulate pancreatic cancer progression and drug resistance**

Pancreatic cancer (PC) has the seventh highest mortality rate among all cancers. It is particularly common in North America, Australia and Europe, and the incidence of PC is higher in males than in females[118]. Several circRNAs have been found to be involved in PC and may be used as therapeutic targets. For example, circBFAR (hasa-circ-0009065) is upregulated in pancreatic ductal adenocarcinoma (PDAC), acting as a miR-34b-5p sponge, and modulates the MET/P13K/Akt signaling pathway[119].

circFOXK2 is likewise upregulated in PDAC and promotes the expression of ANK1, GDNF and PAX6 by acting as a sponge for miR-942, ultimately promoting the prolif-
Table 4 circRNAs involved in esophageal cancer gene transcription regulation and drug resistance

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>circRNA</th>
<th>Gene expression</th>
<th>Mechanism</th>
<th>Drug</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal cancer</td>
<td>circUBAP2</td>
<td>↑</td>
<td>Acts as miR-422 sponge</td>
<td>NR</td>
<td>[108]</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>hsa-circ-0006948</td>
<td>↑</td>
<td>miR-490-3p to enhance HMGA2-induced EMT</td>
<td>NR</td>
<td>[109]</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>circ-0000654</td>
<td>↑</td>
<td>miR-149-5p/IL-6/STAT3 pathway</td>
<td>NR</td>
<td>[110]</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>circGSK3</td>
<td>↑</td>
<td>β-catenin signal passing</td>
<td>NR</td>
<td>[111]</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>circ-Foxo3</td>
<td>↓</td>
<td>miR-23a/PTEN pathway</td>
<td>NR</td>
<td>[112]</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>circPVT1</td>
<td>↑</td>
<td>Acts as miR-4663 sponge</td>
<td>NR</td>
<td>[113]</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>ciRS-7</td>
<td>↑</td>
<td>Acts as a miR-876-5p sponge</td>
<td>Rapamycin</td>
<td>[114,115]</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>circRNA-001275</td>
<td>↑</td>
<td>Acts as a miR-370-3p sponge</td>
<td>Cisplatin</td>
<td>[117]</td>
</tr>
</tbody>
</table>

NR: Not reported; circRNA: Circular RNA.

Overall, circRNAs carry out important roles in tumors. Further studies are expected to serve as new therapeutic targets and biomarkers for tumor diagnosis in the future[134] (Table 5).

**circRNAs PARTICIPATE IN DRUG RESISTANCE**

Following chemotherapy, cancers may relapse, and many patients gradually develop resistance to several anticancer drugs. In the present study, we have summarized findings that report that circRNAs may inhibit or promote tumor growth and migration by acting as miR sponges or other pathways in vitro and in vivo. circRNAs may play the role of vectors in drug resistance due to their unique structure, promoting an inhibitory effect of drugs on tumor cells. Drug resistance of tumor cells involvement of tumor cells. In line with this, knockdown of circFOXK2 was conducive to the inhibition of tumor progression[120]. circ-ADAM9 is highly expressed in PC. It activates the ERK/VEGF signaling pathway via miR-217[121]. circ-ASH2L is also highly expressed in PDAC and acts as a sponge for miR-34a, promoting tumor cell proliferation and tumor progression via regulation of Notch1 in PDAC[122]. circ-LDLRAD3 is also overexpressed in PC and regulates cell proliferation via the miR-137-3p/PTN axis. It affects prognosis of PC and its knockdown inhibits the invasion of tumor cells[123]. circ-0000977 is upregulated in PC and acts as a miR-155 sponge. Knockdown of circ-0000977 conveys the limiting effect of HIF1A and ADAM10 on PC cells under hypoxia[124]. hsa-circRNA-0007334 is upregulated in PDAC and competes for binding with hsa-miR-144-3p[125]. Similarly as in EC, high expression of ciRS-7 promotes PDAC development via acting as an miR-7 sponge and regulating the EGFR/STAT3 signaling pathway. Knockdown of ciRS-7 inhibits the proliferation and invasion of tumor cells[126]. circ-0030235 is upregulated in PDAC and acts as a sponge for miR-1253 and miR-1294. Its expression is a poor prognostic indicator in PDAC[127]. circZMYM2 is also upregulated in PC. It acts as a miR-335-5p sponge and regulates the downstream oncogene RASSF1. Knockdown of circZMYM2 is conducive for the inhibition of tumor growth[128]. circ-0007534 is upregulated in PDAC and acts as a sponge for miR-625 and miR-892b, increasing the proliferation and invasion of tumor cells[129]. circ-IArs is upregulated in PDAC, absorbs miR-122 as a sponge, and increases RhoA activity and F-actin expression, reduces ZO-1 expression, and promotes tumors by enhancing endothelial cell monolayer permeability, invasion and metastasis[130]. Moreover, circ-PDE8A is upregulated in PDAC and acts as a sponge for miR-338, regulating MACC1 expression and promoting the growth of tumor cells via the MACC/MET/ERK or AKT signaling pathways[131].

Gemcitabine is an important drug for the treatment of advanced PC. A study showed 68 upregulated and 58 downregulated circRNAs in gemcitabine-treated PANC-1 cells of which two were significantly upregulated (chr14: 10140210 19101464444+, chr4: 52729603-52780244+)[132]. circHIPK3 is highly expressed in PC and promotes gemcitabine resistance in PC cells by acting as a miR-330-5p sponge and targeting RASSF1[133].

Overall, circRNAs carry out important roles in tumors. Following further studies, they are expected to serve as new therapeutic targets and biomarkers for tumor diagnosis in the future[134] (Table 5).
Table 5 circRNAs involved in pancreatic cancer gene transcription regulation and drug resistance

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>circRNA</th>
<th>Gene expression</th>
<th>Mechanism</th>
<th>Drug</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic</td>
<td>circBFAR</td>
<td>↑</td>
<td>Acts as a miR-34b-5p sponge</td>
<td>NR</td>
<td>[119]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circFOXK2</td>
<td>↑</td>
<td>Acts as miR-942 sponge</td>
<td>NR</td>
<td>[120]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circ-ADAM9</td>
<td>↑</td>
<td>Activate ERK/VEGF signaling pathway through miR-217</td>
<td>NR</td>
<td>[121]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circ-ASH2L</td>
<td>↑</td>
<td>Acts as a sponge for miR-34a</td>
<td>NR</td>
<td>[122]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circ-LDLRAD3</td>
<td>↑</td>
<td>Adjustable via miR-137-3p/PTN axis</td>
<td>NR</td>
<td>[123]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circ-000977</td>
<td>↑</td>
<td>Acts as a sponge for miR-153</td>
<td>NR</td>
<td>[124]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>hsa-circRNA-0007334</td>
<td>↑</td>
<td>Competitive binding through hsa-miR-144-3p</td>
<td>NR</td>
<td>[125]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circ-RS-7</td>
<td>↑</td>
<td>Acts as miR-7 sponge</td>
<td>NR</td>
<td>[126]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circ-0030235</td>
<td>↑</td>
<td>Acts as miR-1253 and miR-1294 sponge</td>
<td>NR</td>
<td>[127]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circZMYM2</td>
<td>↑</td>
<td>Acts as a miR-335-5p sponge</td>
<td>NR</td>
<td>[128]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circ-0007534</td>
<td>↑</td>
<td>Acts as miR-625, miR-892b sponge</td>
<td>NR</td>
<td>[129]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circ-IARS</td>
<td>↑</td>
<td>Acts as miR-122 sponge</td>
<td>NR</td>
<td>[130]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circ-PDE8A</td>
<td>↑</td>
<td>As a sponge of miR-338 to regulate MACC1</td>
<td>NR</td>
<td>[131]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>circHIPK3</td>
<td>↑</td>
<td>Acts as a miR-330-5p sponge</td>
<td>Gemcitabine</td>
<td>[133]</td>
</tr>
</tbody>
</table>

NR: Not reported; circRNA: Circular RNA.

is associated with many factors and the underlying mechanisms are complex. Resistance mechanisms conveyed by circRNAs may be related to glycolysis, ATP levels, or other factors. With regard to the preliminary results of studies on drug resistance, several mechanisms and pathways have been reported to be involved in the regulation of drug resistance by circRNAs in esophageal, pancreatic, colon, liver and gastric cancer. Although further exploring the mechanisms may enable the development of preventive mechanisms against drug resistance among cancer cells, there is still a long way to go for understanding circRNAs and tumor drug resistance (Figure 3).

CONCLUSION

There is currently a lack of monitoring methods and treatment tools for the development of gastrointestinal tumors and the occurrence of drug resistance. The pathogenesis of gastrointestinal tumors is diverse, including many unstable factors such as DNA damage repair, genome instability and mutations, gene transcription regulation, chromosome modifications, inflammation, tobacco and alcohol, obesity, and autoimmunity. circRNAs exert rich biological functions and play an important role in gastrointestinal tumors. This article discusses the mechanisms of tumor development and drug resistance of gastrointestinal tumors related to circRNAs. While the exact mechanisms of involvement of circRNAs have not been fully elucidated, their important roles in various tumors as observed in initial studies have attracted a lot of attention and have huge potential for future clinical approaches. With advances in biotechnology, new applications such as genetic testing, polymerase chain reaction, high-throughput sequencing, and in-depth research in gastrointestinal tumors, it is expected that circRNAs could be developed into diagnostics or therapeutic targets for the treatment of gastrointestinal tumors. In case circRNAs can become a mass-produced product due to technological innovation, they could be used for clinical treatment. Noninvasive detection distinguishing malignant and benign tumors may also be enabled via biotechnological advances. Other options could include the development of new prognosis indicators for patients and monitoring of drug sensitivity, all aimed to ultimately extend patient life and disease-free survival. Based on the presented literature, there is hope that circRNAs may become an effective therapeutic target for cancer treatment in the future.
Figure 3  Circular RNAs have a regulatory effect on gastrointestinal tumors via signaling molecules, and have been shown to influence drug resistance in gastric, liver, intestinal, esophageal, and pancreatic cancer.

REFERENCES


Xi SJ et al. circRNAs in gastrointestinal tumors and drug resistance


Xi SJ et al. circRNAs in gastrointestinal tumors and drug resistance


Gao X, Zhou Q, Su D, Luo Y, Fu Z, Huang L, Li Z, Jiang D, Kong Y, Chen R, Chen C. Circular RNA circBFAR promotes the progression of pancreatic ductal adenocarcinoma via the miR-34b-
Breast Cancer
Zhang HD
Liu Y
10.3389/fphar.2018.00584
Pancreatic Ductal Adenocarcinoma.
Shao F
10.1016/j.canlet.2018.04.035
pathway in pancreatic cancer.
released exosomal circular RNA PDE8A promotes invasive growth
Li Z
30064461
cells and located within exosomes regulates endothelial
monolayer permeability to promote tumor metastasis.
IARS) secreted by pancreatic cancer cells and located within exosomes regulates
endothelial
promotes the proliferation and metastasis of pancreatic cancer by regulating miR-7-mediated
Xu Y
30898507
axis.
mediated immune escape of pancreatic cancer cells from NK cells: role of circ_0000977/miR-153
Ou ZL
31521692
pancreatic cancer progression through miR-137-3p/PTN axis.
Pancreatic ductal adenocarcinoma.
ASH2L promotes tumor progression by sponging miR-34a to regulate Notch1 in pancreatic ductal
expression.
Xiong C
10.1158/0008-5472.CAN-19-3260
Metastasis of Pancreatic Ductal Adenocarcinoma by Complexing with RNA-Binding Proteins and
miR-942.
Liver injury associated with acute pancreatitis: The current status of clinical evaluation and involved mechanisms

Wei Liu, Juan-Juan Du, Zeng-Hui Li, Xin-Yu Zhang, Hou-Dong Zuo

Author contributions: Liu W wrote the paper; Du JJ, Li ZH, and Zhang XY reviewed the literature; Zuo HD 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.

Country/Territory of origin: China

Specialty type: Radiology, nuclear medicine and medical imaging

Provenance and peer review: Invited article; Externally peer reviewed.

Abstract
Acute pancreatitis (AP) is a very common acute disease, and the mortality rate of severe AP (SAP) is between 15% and 35%. The main causes of death are multiple organ dysfunction syndrome and infections. The mortality rate of patients with SAP related to liver failure is as high as 83%, and approximately 5% of the SAP patients have fulminant liver failure. Liver function is closely related to the progression and prognosis of AP. In this review, we aim to elaborate on the clinical manifestations and mechanism of liver injury in patients with AP.

Key Words: Acute pancreatitis; Liver injury; Liver dysfunction; Cytokines; Oxidative stress

Core Tip: Several studies have contributed to the pathophysiology and clinical trials of liver dysfunction associated with acute pancreatitis (AP). However, great progress has been made on liver injury-associated AP (LIAAP) based on the published literature. This review aims to summarize the research progress of LIAAP’s clinical manifestations and underlying mechanisms, which can provide new insights for further understanding and better treatment of AP and LIAAP.

Citation: Liu W, Du JJ, Li ZH, Zhang XY, Zuo HD. Liver injury associated with acute pancreatitis: The current status of clinical evaluation and involved mechanisms. World J Clin Cases 2021; 9(34): 10418-10429

URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10418.htm

DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10418
Acute pancreatitis (AP) is a common disease that often requires hospitalization. Over the past decades, as knowledge of pancreatitis has increased, the death rate of pancreatitis has decreased dramatically, but the mortality rate of patients with organ failure during severe AP (SAP) is still high. Global estimates of the incidence and mortality rate for AP were 33.74 cases (95% CI: 23.33-48.81) per 100000 people and 1.60 deaths (95% CI: 0.85-1.58) per 100000 people each year [1]. SAP, characterized by severe progression and numerous complications, often leads to a high mortality rate due to hypermetabolism, systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome (MODS). Death from AP mainly occurs in two peaks: the first peak appears early and is related to the development of MODS in the first week after the initial onset, and the second peak of death is closely related to infections [2]. Even for those patients who did not progress to MODS, the incidence and severity of liver injury were positively correlated with the severity of AP, which prolonged the course of AP. The liver is the largest concentration of macrophages (Kupffer cells, KCs) in the body; therefore, it is very important in the control of systemic endotoxemia, bacteremia, and vasoactive byproducts. According to a previous report, the mortality rate of patients with SAP related to liver failure is as high as 83% [3]. Thus, it is crucial for us to understand the relationship between liver injury and AP. This review aims to delineate the clinical manifestations and to illustrate the current understanding of the mechanisms of liver injury-associated AP (LIAAP).

EFFECTS OF AP ON THE LIVER

AP can cause damage to the liver [4]; however, liver injury can also aggravate the severity of AP [5]. LIAAP often presents with abnormal serum biochemical indicators, abnormal liver perfusion, and fatty liver.

Serum biochemical indexes of liver function

In AP, the serum biochemical indexes of the liver often change, and changes in liver function will affect the severity and prognosis of AP.

The level of serum bilirubin reflects the ability of hepatocytes to uptake, bind, and excrete bilirubin through the liver reticuloendothelial system. When the hepatocytes are damaged, the ability of the liver to clear bilirubin is decreased, and the level of blood bilirubin is increased. When the level of bilirubin in serum is too high, the patient will develop jaundice. Serum total bilirubin, albumin (ALB), and ALB-bilirubin scores are independent risk factors for SAP and can predict hospital mortality in SAP [6,7].

The increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) usually indicates the severity of the liver disease, which usually precedes the appearance of abnormal clinical symptoms, but with the aggravation of liver injury, a large number of hepatocytes become necrotic and die, eventually causing aminotransferase to become exhausted. Consequently, the decrease in aminotransferase occurs in the severe stage of severe liver disease, so the elevated level of the aminotransferase cannot accurately reflect the severity of liver disease or be used to evaluate the prognosis [8]. The serum levels of ALT and AST are positively correlated with the severity of pancreatitis, and the serum levels of ALT and AST return to normal after pancreatitis is resolved [9].

Serum ALB is only synthesized by the liver, with a half-life of 20 d, which can reflect the synthetic function of the liver within a certain period of time. When a large number of hepatocytes are necrotic and the residual function cannot be fully compensated, the level of ALB may decrease. ALB is an independent prognostic factor of persistent organ failure (POF) and can predict POF in AP [10].

Prothrombin time (PT) can be an indicator of the function of the exogenous coagulation system. When severe liver parenchymal cell damage occurs, it can lead to the disturbance in the synthesis and biological activities of coagulation factors I, II, V, VII, and X, which results in the prolongation of PT. Dynamic changes in coagulation and fibrinolytic markers (such as PT) are good predictors of AP-related mortality and organ failure in patients with AP [11].

Alkaline phosphatase (ALP) mainly exists in the bile capillaries of the liver, bone, kidney, and placenta, while γ-glutamyl transpeptidase (GGT) mainly exists in the cell membrane of the liver, pancreas, spleen, kidney, heart, and brain. The presence of liver parenchymal damage, cholestasis, or biliary obstruction from the capillary bile duct to
any level of common bile duct opening can lead to an increase in ALP and GGT. In
gallstone AP, patients with higher levels of ALT, bilirubin, and ALP had longer
hospital stays than patients without these elevations[12].

**Fatty liver in AP**

Fatty liver and AP also interact with each other. Researchers have retrospectively
collected data from patients with AP after a magnetic resonance (MR) examination and
found that there was a significant correlation between the difference in liver signal
intensity on in-phase (IP)/out-phase (OP) images and the MR severity index (MRSI)
score in AP patients with fatty liver. The difference in liver signal intensity increased
with an increasing MRSI score. During the follow-up, it was found that fatty liver
could disappear or be relieved after the patient recovered. On the one hand, fatty liver
occurs or is aggravated in AP; on the other hand, fatty liver also improves after AP
improves[4]. In AP, the incidence of complications, organ failure, metabolic disorder,
SIRS, infection, death, and hospital stay were increased in patients with fatty liver[5,
13-16] (Figure 1A-D).

**Liver perfusion abnormalities in AP**

There is a correlation between the blood perfusion noted on computed tomography
(CT) and the severity of liver injury[17], and there are obvious perfusion changes in
liver tissue caused by AP. In perfusion changes, systemic mediators seem to be as
effective as local inflammatory changes[18]. It has been reported that a perfusion CT
performed within the first 24 h after the onset of AP can predict the severity of AP by
revealing liver perfusion abnormalities[19].

The inflammatory process of AP may spread through the hepatoduodenal ligament
or the gastrohepatic ligament to the hilum to the liver and eventually along the Glisson
sheath[20,21]. Liver perfusion abnormalities in AP may be caused by an increase in the
arterial blood flow due to inflammation of the liver lobes or gallbladder[22]. AP can
spread to the vesicle and can easily enter the left lobe of the liver around the gastro-
hepatic ligament because the pancreatic body is usually close to the left lobe of the
liver[23]. However, an interesting finding is that in an experiment in rats with AP
induced by the intraperitoneal administration of caerulein, perfusion changes were
more obvious in the right lobe[18]. This has also been demonstrated in human patients
[24]. Perfusion changes may be dependent not only on local inflammatory processes
but also on the effect of systemic mediators. At the end of the experiment, the rats
were euthanized, the liver was resected, and the liver tissue was sent for histopatho-
logical analysis. The results showed hepatocyte destruction, sinusoid dilatation, focal
carcinosis, KCs proliferation, and central venous congestion. It can be seen from this that
systemic mediators seem to have effects similar to the local inflammatory changes in
regards to perfusion[18]. Finally, liver perfusion abnormalities in AP may be related to
a low blood volume and the high metabolism caused by the inflammation. Portal
venous blood flow decreases by 50% in AP and increases by 50% after fluid
resuscitation. Visceral insufficiency is present in the early stages of acute hemorrhagic
pancreatitis, and signs of insufficient blood perfusion can be prevented by fluid
resuscitation[25]. Liver blood volume is estimated to be 1/4 of the cardiac output and
is important for maintaining a normal liver function. A decreased perfusion within the
liver impairs and inhibits the function of the blood/hepatocyte replacement process
(Figure 1E and F).

In addition, the ratio of liver volume measured by CT to the standard liver volume
reflects the changes in the liver volume during the occurrence and development of the
acute liver failure, and this ratio can be used to judge the prognosis of the acute liver
failure. The results show that in acute liver failure, CT-derived liver volume/
standardized liver volume measured by CT < 83.9% indicates a poor prognosis[26].
Whether LIAAP will cause changes in liver volume needs further study.

**THE KEY REGULATORY FACTORS AND UNDERLYING MECHANISMS**

In AP, MODS is closely related to the prognosis of the disease, and the liver is one of
the key extrapancreatic organs. For patients with LIAAP, the treatment of the liver
injury can also improve the prognosis of AP. Therefore, it is urgent to determine the
potential mechanisms of LIAAP.
Cytokine and inflammatory cascade, inflammatory mediator

Cytokines are divided into proinflammatory and anti-inflammatory cytokines, which are balanced with each other[27]. According to the theory of the inflammatory-anti-inflammatory factor balance, when the body is subjected to a harmful stimulation, the inflammatory response is activated as the protective mechanism of the body by releasing pro-inflammatory cytokines, and the anti-inflammatory system is also activated. The body releases anti-inflammatory cytokines to inhibit and regulate the inflammatory response. This not only makes the body effectively resist the invasion of pathogenic factors but also prevents the overactivation of the inflammatory reaction to prevent alterations of the normal function of the body.

During the progression of AP, activated digestive enzymes attack pancreatic acinar cells and hepatocytes. At the same time, activated digestive enzymes can induce neutrophils to release a large number of inflammatory factors, which can lead to a systemic inflammatory response, thus causing damage to multiple organs. Pancreatic elastase induces KCs to produce cytokines by activating the nuclear transcription factor-κB (NF-κB) pathway during SAP[28]. Because part of the pancreatic blood flows back through the portal vein, the liver is the first extrapancreatic organ attacked by high concentrations of activating enzymes and inflammatory mediators at the beginning of AP.

Tumor necrosis factor-α: Excessive tumor necrosis factor-α (TNF-α) can activate neutrophils and release interleukin-1 (IL-1) β, IL-6, IL-8 and other cytokines, which leads to a wide range of pathological reactions. TNF-α is an important initiator of SAP complications, including liver damage. The mechanisms of liver injury induced by TNF-α include: (1) Direct hepatotoxicity; (2) An excessive production of nitric oxide (NO) and an excessive production of oxygen free radicals (OFR) by hepatic KCs and neutrophils, leading to cytotoxic effects; and (3) Apoptosis of hepatocytes and KCs induced by endotoxin before cell injury. TNF-α alone can cause toxic shock symptoms and lead to MODS[29,30].

IL-6: In AP, IL-6 can promote the activation of B lymphocytes and eventually increase the synthesis of immunoglobulins to promote humoral immunity, promote the proliferation and differentiation of T lymphocytes, and promote acute phase reactions, which lead to liver tissue injury, an increase neutrophil function, and induce intercellular adhesion factor-1 to recruit neutrophils from the liver to the damaged liver tissue. The activation of IL-6 also promotes leukocytes to stay in the vascular system of the liver and adhere to the surface of endothelial cells. The leukocytes release toxic
substances, such as elastase and ORF, to directly damage the liver vascular endothelium in AP[31].

**IL-8:** IL-8 is a neutrophil chemokine produced mainly by neutrophils that mediates inflammation from the pancreas to extrapancreatic organs, such as the liver. IL-8 increases the tissue damage of neutrophils and enhances the phagocytosis and killing effect of NK cells on inflammatory tissues[31].

**IL-18:** IL-18 belongs to the IL-1 superfamily and is produced mainly by macrophages but also by other cell types. It stimulates various cell types and has pleiotropic functions. IL-18 is a proinflammatory cytokine that triggers a type 1 response. Together with IL-12, it induces cell-mediated immunity after exposure to microbial products, such as lipopolysaccharide (LPS)[32]. IL-18 mediates liver damage through two mechanisms: (1) Inducing Fas ligand (FasL) expression to directly mediate hepatocyte apoptosis; and (2) Through the Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling pathway[32].

**High-mobility group box-1:** High mobility group protein B1 (HMGB1) is a highly conserved nuclear protein that is widely distributed in mammalian cells. Mechanically damaged and necrotic cells can release HMGB1 from the nucleus extracellularly to induce an inflammatory response. The coexistence of damaged cells and macrophages can cause NF-κB-induced nuclear transfer of macrophages and produce an inflammatory response similar to that caused by tissue necrosis[33]. Ethyl pyruvate (EP) may have a therapeutic effect on LIAAP by regulating the response of box 1 and other inflammatory cytokines in the high mobility group, which indicates that LIAAP may be related to HMGB1[34].

During SAP, the liver function is affected by the pancreatitis. The liver’s ability to remove toxic and biologically active substances is significantly reduced, and it loses its barrier function to prevent endotoxemia, leading to excessive release of endogenous inflammatory mediators, which forms a vicious cycle. A large number of endogenous inflammatory mediators then enter the systemic circulation, causing a continuous systemic inflammatory response, systemic tissue damage, and organ dysfunction. The resulting chain reactions and amplification reactions are called cascade reactions, which lead to SIRS and MODS[35,36].

**Microcirculation disturbances**

Microcirculation disturbances are an important pathological process of AP[37]. In the early stage of AP, microcirculatory disorders can occur in the pancreas and liver[38]. Disorders of microcirculation are an important cause of SAP combined with liver injury. In SAP, liver injury is associated with an insufficient blood volume due to the release of vasoactive substances and the insufficient blood circulation to the liver. A decrease in liver blood flow can cause mitochondrial ATP synthesis disorders, and the phosphorylation rates of cytochrome A and B are also decreased[39]. Endothelin (ET) and NO play opposite roles in the regulation of blood flow, and the regulation of ET and NO on blood vessels is in a dynamic balance. TXA2/PGI2 is a pair of vasodilator regulators, and imbalances of these factors can cause pathological changes, such as vasomotor disorder, microthromboses, vascular occlusion, and so on. In LIAAP, the balance of TXA2/PGI2 and ET/NO is damaged. The relationship between liver injury, the vascular endothelial cell secretion of ET and NO, and the arachidonic acid metabolites, thromboxane (TXA2) and prostacyclin (PGI2), have been described[31].

Tissue factor (TF), also known as platelet TF, factor III, or CD142, is a protein encoded by the F3 gene and is present in the subcutaneous tissue and the white blood cells but is mainly expressed in extravascular tissues[40,41]. TF is the main cellular initiator for coagulation due to its interaction with coagulation factor VII[42]. Both the coagulation system and the fibrinolytic system can be activated during AP, but the function of the fibrinolytic system is relatively insufficient[43]. In SAP, monocytes stimulated by LPS, TNF-α or IL-1 can produce high levels of TF expression. TF can be transferred to platelets and participate in the process of pathological coagulation, and an abnormal expression of TF leads to a dysfunction of the blood coagulation system. In the KCs of the SAP mouse model, the expression of TF was also highly upregulated. After the inhibition of KCs, the function of the coagulation system was improved, the levels of serum TF and TF microparticles (TF-mps) were decreased, and SAP-related liver injury was alleviated[43]. The imbalance of TF expression plays an important role in the process of liver injury caused by liver microcirculation disturbances.
Fibrinogen-like protein 2 (FGL2) is a 70 kDa glycoprotein that belongs to the fibrinogen-related superfamily and is involved in blood coagulation, cell adhesion, and transendothelial migration[44]. In SAP, the FGL2 prothrombin gene and protein expression were significantly upregulated. Fgl2 prothrombin is involved in the development of microthromboses, which leads to the disturbance of liver microcirculation and eventually leads to liver injury[45].

Disturbance of the microcirculation of the pancreas and liver not only affects the blood supply of other organs, but also leads to an increase in the concentration of inflammatory factors and active peptides in the tissue and cells, which further aggravates the ischemic and hypoxic state of the cells and tissues of the pancreas and liver. These mechanisms further worsen the functional damage of the pancreas and liver.

**Oxidative stress**

Oxidative stress is a state of imbalance between oxidation and the antioxidant activity in the body, with a bias toward oxidation, which results in the inflammatory infiltration of neutrophils, an increase in protease secretion, and the production of large amounts of oxidative intermediates. Oxidative stress is a negative effect produced by free radicals in the body and is considered to be an important factor in aging and disease[46]. Oxidative stress can also cause liver injury through a variety of mechanisms[47-49]. Reactive oxygen species (ROS), including oxygen ions, peroxides, and oxygen-containing free radicals (OFRs), are a byproduct of biological aerobic metabolism. Under physiological conditions, there is a balance between the production of ROS and their elimination through the mechanism of endogenous antioxidants[50]. In AP, the balance between the oxidant and antioxidant system is damaged. In an animal experimental model, a large amount of OFR is produced in the early stage of AP induced by a duct obstruction in rats[51]. Highly active ROS directly attack lipids and proteins in biofilms and cause their dysfunction[52]. Excessive ROS production can oxidize lipids in the cell membrane, proteins in the cell solute, DNA and other macromolecules in the nucleus. When activated leukocytes increase the production of ROS in AP, the intrinsic defense mechanism leads to cytoskeletal alterations and cell membrane damage in acinar cells[53]. The destruction of the cytoskeleton interferes with the transport of digestive enzymes in cells and activates digestive enzymes prematurely in acinar cells[54]. Cell fragmentation and leakage of ROS and activated pancreatic enzymes damage the capillary endothelium, increase the capillary permeability, and lead to tissue edema. Malondialdehyde (MDA) is an oxidation product produced by the OFR after interacting with fat in the body and can be used as a sign of the degree of oxidative damage[55]. The reaction between MDA and DNA leads to mutations or protein reactions, which leads to changes in DNA and protein structure and function, which causes damage to the cell membrane and then damage to hepatocytes. The accumulation of MDA induces a change in mitochondrial membrane permeability, which promotes the release of many apoptosis-related cytokines, such as cytochrome C, apoptosis-inducing factor, and endonuclease G, and finally leads to apoptosis. In animal experiments, researchers have found that in caerulein-induced AP mice, the activity of superoxide dismutase in the pancreatic tissue was decreased, and the concentration of MDA in the pancreatic tissue was significantly increased. Studies have shown that OFR mediate the increase in lipid peroxidation in pancreatic tissue[56]. Caerulein-induced pancreatitis and liver damage are accompanied by a significant increase in the tissue MDA levels. These findings suggest that lipid peroxidation is significantly enhanced not only in the pancreatic tissue but also in the liver tissue. Therefore, lipid peroxidation should be one of the mechanisms of liver injury caused by oxidative stress[57]. Oxidative stress-induced hepatocyte apoptosis is affected by a variety of regulatory mechanisms, including mitogen-activated protein kinase (MAPK), NF-κB, caspase, Bcl-2, and the death receptor (DR)[58]. NLRP3 also appears to be regulated by ROS, and LIAAP may be related to NLRP3[59]. The NLRP3 inflammatory bodies mainly induce IL-1β and aggravate inflammatory liver injury[60].

Based on the mechanisms of liver injury induced by oxidative stress, the antioxidant effects of melatonin, thalidomide, carvol, ascorbic acid, N-acetylcysteine, and L-cysteine can help ameliorate the liver injury induced by AP[57,61-64].

**Endotoxin**

In AP, endotoxin also plays an important role in liver injury[65]. Pancreatitis causes a disruption in the intestinal function, reduces the function of the intestinal barrier, and disrupts the intestinal microenvironment and normal flora, and endotoxin then enters the bloodstream and invades the liver through the circulation. The endotoxin entering
the liver activates phospholipase A2 (PLA2) to mediate membrane phospholipid degradation and induce free radicals to mediate lipid peroxidation in liver cells[66]. In addition, it also causes liver damage by interfering with energy metabolism. The Toll-like receptor 4 (TLR4) signaling pathway, transforming growth factor β1 (TGF-β1), and p38 MAPK signaling pathways are involved in the occurrence of PALI[67-69].

**Signaling pathways**

Signaling pathways refer to a series of enzymatic reaction pathways that can transfer extracellular molecular signals into the cell through the cell membrane. These extracellular molecular signals (called ligands) include hormones, growth factors, cytokines, neurotransmitters, and other small molecular compounds. NF-κB, JAKSTAT and P38MAPK are mainly involved in the signaling pathways related to LIAAP.

**NF-κB**: NF-κB is an important nuclear transcription factor in cells. NF-κB participates in the inflammatory response and the immune response and can regulate apoptosis and the stress response. NF-κB is one of several key signaling systems that mediate the proinflammatory signal in AP[70], so it may become a target for drug therapy in inhibiting the NF-κB signal transduction pathway[71]. AP induces liver injury by upregulating Fas/FasL derived from KCs[72]. On the other hand, AP induces KC apoptosis through an NF-κB-dependent pathway. The balance between the upregulated expression of Fas/FasL and the initial apoptosis induced by Fas/FasL may determine the severity of the pancreatitis-related liver injury[73].

**JAK-STAT**: The JAK-STAT signaling pathway is involved in many important biological processes, such as cell proliferation, differentiation, apoptosis, and immune regulation. Compared with other signaling pathways, the transmission process of this signaling pathway is relatively simple, and it is mainly composed of three components, namely, the tyrosine kinase-related receptor, the tyrosine kinase JAK, and the transcription factor STAT[74].

The JAK-STAT signaling pathway constitutes one of the major pathways for cytokine signal transduction. Researchers found that in SAP rats induced by a retrograde infusion of 4% sodium taurocholate into the cholangiopancreatic duct, the levels of the liver enzymes, TNF-α, IL-6, and IL-18 were all significantly increased, and the protein expression levels of JAK2 and STAT3 were significantly increased. In the SAP with AG490 (inhibition of JAK2) group, AG490 effectively inhibited the activation of JAK2 and STAT3 phosphorylation, the levels of liver enzymes TNF-α, IL-6, and IL-18 were significantly decreased, and the protein expression levels of JAK2 and STAT3 were significantly decreased. This suggests that the activation of JAK2/STAT3 gene expression and the production of inflammatory factors such as TNF-α, IL-6, and IL-18 can lead to a pancreatitis-induced liver injury[75].

**P38 MAPKs**: P38 MAPKs are a family of MAPKs that respond to stress stimuli (such as cytokines, ultraviolet radiation, heat shock, and osmotic shock) and are involved in cell differentiation, apoptosis, and autophagy. Due to aging, the continuous activation of the p38 MAPK pathway in muscle satellite cells (muscle stem cells) can inhibit muscle regeneration[76,77]. Studies have shown that p38 MAPK plays an important role in the pathogenesis of SAP[78]. P38 MAP kinase modulates the activation of the NF-κB pathway in AP. In addition, KCs can amplify the release of cytokines by activating p38 MAPK, which leads to the liver injury in AP. Therefore, the activation of p38 MAPK in KCs may be the main regulatory mechanism of SAP[79,80].

**Hepatocyte apoptosis**

Hepatocyte apoptosis may be one of the factors leading to liver failure. The roles of liver Bax, Bcl-2, IL-1 inversase inhibitors, and TGF-β1 in liver injury induced by SAP hepatocyte apoptosis have been previously reviewed[31].

The Ca²⁺ storage site in the endoplasmic reticulum (ER) in cells is the largest membrane organelle in the cell and controls the processing, modification, and synthesis of a large number of proteins in the cell. When the environment in the ER, which is characterized by oxidation and a high calcium concentration, is destroyed, it leads to the accumulation of incorrectly folded proteins in the ER, which leads to severe ER stress (ERS)[81,82]. ERS is a new pathway that is different from the mitochondrial pathway and can independently lead to apoptosis. ERS plays an important role in the occurrence and development of the liver injury induced by AP[83].
THE CLINICAL MANAGEMENT OF LIAAP

The treatment of AP includes close monitoring of vital signs, fluid resuscitation, nutrition, pain management, prevention of secondary infections, and management of local complications[84]. The treatment of LIAAP is closely related to the treatment of AP because the degree of liver damage depends on the severity of the pancreatitis. According to the mechanism of LIAAP, treatment methods include anti-inflammatory and antioxidant therapies, the improvement of the microcirculation, the inhibition of apoptosis, the promotion of liver cell regeneration, and supportive therapy.

In the rat model, sodium butyrate can inhibit the activation of NF-κB in the liver, reduce the expression of the HMGB1 gene, reduce the level of the HMGB1 protein, and ultimately reduce the lethal outcome of SAP rats[33]. Antioxidants, such as melatonin, ascorbic acid, and N-acetyl cysteine, reduce the damage to the pancreas and liver during AP by restoring the activity of tissue antioxidant enzymes[37]. Recombinant human soluble thrombomodulin and prostaglandin E1 reduce liver and pancreas damage by maintaining the microcirculation, which improves the prognosis of SAP[85,86]. Nilotinib reduces pancreatic and liver damage through antioxidant and anti-inflammatory effects[87]. Heme oxygenase-1 can prevent pancreatic and liver damage through antioxidation, the maintenance of the microcirculation, and anti-inflammatory mechanisms[88]. When SAP is complicated by liver and kidney injuries, the level of vascular endothelial cell growth factor (VEGF) is increased. The administration of recombinant VEGF to an SAP rat model can effectively improve the liver and kidney function and significantly inhibit cell apoptosis in the liver and kidney[89]. Somatostatin can inhibit the overexpression of serum TNF-α mRNA in AP rats and reduce the pancreatic and liver tissue damage[90]. EP significantly reduces serum ALT and liver necrosis in the SAP mouse model through anti-inflammatory and antioxidant effects[91].

Because of the influence of multiple factors in the course of AP, the combined use of the above drugs may improve the prognosis. In addition to supportive therapy, treatment of the pancreas and the extrapancreatic organs is also a promising treatment method, but further research is needed.

CONCLUSION

The clinical manifestations of LIAAP are usually the presence of abnormal serum biochemical indexes and abnormal liver perfusion. There are many reasons for AP complications and secondary liver injury. These factors cooperate and cause cascade reactions, which lead to the liver injury. Treatment of the liver injury can alleviate the severity of AP. Finally, a new mechanism of LIAAP may be found through proteomics and metabolomics, and further related studies are needed.

REFERENCES

DOI: 10.7150/ijims.49606
Liu W et al. Liver injury associated with acute pancreatitis


34 Luan ZG, Zhang H, Ma XC, Zhang C, Guo RX. Therapeutic treatment with ethyl pyruvate attenuates the severity of liver injury in rats with severe acute pancreatitis. Pancreas 2012; 41: 729-737 [PMID: 22699144 DOI: 10.1097/MPA.0b013e31823d8ef]


43 Ou ZB, Miao CM, Ye MX, Xing DP, He K, Li PZ, Zhu RT, Chen T. L-glutamine on oxidative stress, DNA damage, cell viability and hepatotoxicity induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in rat hepatocyte cultures. Cytotechnology 2012; 64: 687-699 [PMID: 22456282 DOI: 10.1007/s10620-012-9449-y]


48 Turkez H, Geykoglu F, Yousefi MF, Celik K, Bakir TO. Ameliorative effect of supplementation with L-glutamine on oxidative stress, DNA damage, cell viability and hepatotoxicity induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in rat hepatocyte cultures. Cytotechnology 2012; 64: 687-699 [PMID: 22453904 DOI: 10.1007/s10620-012-9449-y]


Liver injury associated with acute pancreatitis


78 Twale E, Williard DE, Samuel I. Dominant negative p38 mitogen-activated protein kinase expression


Association between celiac disease and vitiligo: A review of the literature

Jing-Zhan Zhang, Dilinuer Abudoureyimu, Man Wang, Shi-Rong Yu, Xiao-Jing Kang

ORCID number: Jing-Zhan Zhang 0000-0002-2813-4962; Dilinuer Abudoureyimu 0000-0002-8058-141X; Man Wang 0000-0003-2726-7218; Shi-Rong Yu 0000-0002-0884-9987; Xiao-Jing Kang 0000-0002-6683-0707.

Author contributions: Zhang JZ designed the study and drafted the article; Abudoureyimu D, Wang M, Yu SR and Kang XJ revised the article critically for important intellectual content; all the authors approved the version to be published.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

Supported by: National Natural Science Foundation of China, No. 81760563.

Country/Territory of origin: China

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review report’s scientific quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0

Jing-Zhan Zhang, Dilinuer Abudoureyimu, Shi-Rong Yu, Xiao-Jing Kang, Department of Dermatology, People’s Hospital of Xinjiang Uygur Autonomous Region, Xinjiang Key Laboratory of Dermatology Research, Urumqi 830001, Xinjiang Uygur Autonomous Region, China

Man Wang, Department of Gastroenterology, People’s Hospital of Xinjiang Uygur Autonomous Region, Urumqi 830001, Xinjiang Uygur Autonomous Region, China

Corresponding author: Xiao-Jing Kang, MD, PhD, Chairman, Chief Doctor, Professor, Department of Dermatology, People’s Hospital of Xinjiang Uygur Autonomous Region, Xinjiang Key Laboratory of Dermatology Research, NO. 91 Tianchi Road, Tianshan District, Urumqi 830001, Xinjiang Uygur Autonomous Region, China. drkxj@sina.com

Abstract
Celiac disease (CD) is an autoimmune intestinal disease caused by the intake of gluten-containing cereals and their products by individuals with genetic susceptibility genes. Vitiligo is a commonly acquired depigmentation of the skin; its clinical manifestation are skin patches caused by localized or generalized melanin deficiency. Both diseases have similar global incidence rates (approximately 1%) and are associated to similar diseases, including autoimmune bullous disease, inflammatory bowel disease, autoimmune thyroiditis, autoimmune gastritis, and type 1 diabetes. The relationship between CD and vitiligo has been reported in several studies, but their conclusions are inconsistent. Further, it has also been reported that a gluten-free diet (GFD) can improve the symptoms of immune-related skin diseases such as vitiligo. In this mini-review, we summarize and review the literature on the relationship between CD and vitiligo, assess the therapeutic significance of GFD for patients with vitiligo, and explore their possible physiopathology. We are hopeful that the information summarized here will assist physicians who treat patients with CD or vitiligo, thereby improving the prognosis.

Key Words: Celiac disease; Gluten-free diet; Vitiligo; Dermatitis herpetiformis

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
Core Tip: Both celiac disease (CD) and vitiligo are autoimmune-related diseases, and their global incidence rates are similar (approximately 1%). This article reviews recent studies on the relationship between CD and vitiligo, and gluten-free diet (GFD) and vitiligo and explores their possible pathogenesis. An analysis based on existing evidence supports the association between CD and vitiligo. Patients with vitiligo and positive serum gluten markers, or with CD, may benefit from a GFD; it could be a valid option depending on the patient's preference. We hope this review will be useful for future treatment.

URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10430.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10430

INTRODUCTION
Celiac disease (CD) is an autoimmune intestinal disease caused by the intake of gluten-protein containing cereals and its products by individuals with genetic susceptibility genes. The disease can lead to intestinal mucosal damage, mainly manifested as abdominal pain, diarrhea, and other gastrointestinal symptoms. It can also lead to extraintestinal symptoms caused by secondary malnutrition and is associated with an increase in mortality[1]. The global prevalence of CD is approximately 1.4%, and it is gradually increasing[2]. The detection of anti-tissue transglutaminase immunoglobulin A (anti-tTG IgA), anti-endomysial antibody (EMA), and anti-gliadin antibody plays an important role in the diagnosis of CD[3-5]. Anti-tTG IgA is considered the first choice for the serological examination of CD. However, duodenal mucosal biopsy remains the gold standard for the diagnosis of CD[6].

Vitiligo is a commonly acquired depigmentation of the skin that clinically manifests as skin patch caused by localized or generalized melanin deficiency[7]. It is considered an autoimmune disease, although its pathogenesis is not clear and is affected by multiple factors, including autoimmunity, oxidative stress, and genetic susceptibility[8,9]. The incidence rate of vitiligo worldwide is 0.5%–2.0%[10].

Many studies have confirmed that CD and vitiligo are associated with a variety of autoimmune diseases, including autoimmune bullous disease, inflammatory bowel disease, autoimmune thyroiditis, autoimmune gastritis, and type 1 diabetes[11-17]. The relationship between CD and some immune-related skin diseases has been studied and confirmed, but its relationship with vitiligo is controversial. For example, some studies have shown that the incidence of vitiligo in patients with CD is higher than that in patients without CD[18,19]. However, the study by Volta et al[20] did not find any correlation between these two immune diseases[20]. Further, a gluten-free diet (GFD) has been reported to improve the symptoms of patients with immune-related skin diseases, such as dermatitis herpetiformis (DH), psoriasis, and vitiligo, who are seropositive for CD-related autoantibodies[21-23]. The purpose of this mini-review was to explore the relationship between CD and vitiligo, assess the therapeutic significance of GFD for patients with vitiligo, and investigate the underlying mechanisms.

LITERATURE ANALYSIS
We reviewed the literature on the role of CD and gluten in vitiligo. We searched the PubMed, Ovid, Web of Science and Cochrane databases for published articles from their inception to February 2021. The search terms used were "celiac disease" or "gluten-free diet" and "vitiligo." We first screened the titles and abstracts to select potential studies and, then, performed a full-text review. We also reviewed the references in the selected articles to identify any other relevant studies. We included cohort studies, cross-sectional studies, case-control studies, reviews, and case reports that studied the relationship between vitiligo and CD. The duplicates were then removed. If the article lacked clinical relevance or the full text was not available, it was
CLINICAL CHARACTERISTICS

Study characteristics
After a literature search, 878 studies were included, of which 102 duplicates were excluded. There was no restriction based on language.

Vitiligo and the incidence of CD
Four studies, including two case-control and two cross-sectional studies, investigated the incidence of CD in patients with vitiligo. One cross-sectional study investigated the incidence of CD in 176 patients with vitiligo; five (2.8%) of these patients were diagnosed with CD[24]. Further, in a case-control study, Seyhan et al.[25] assessed serum anti-endomysial IgA antibody in 61 patients with vitiligo (21 children) and 60 controls. Eleven patients with vitiligo and one control were positive, and among these seropositive patients, five were younger than 18 years of age. The seroprevalence rates for children and adults were 23.8% and 15%, respectively. Seropositive patients underwent endoscopic duodenal biopsy of the upper gastrointestinal tract, and the prevalence of CD confirmed by biopsy was 3.2%[25]. The second case-control study by Shahmoradi et al.[16] assessed EMA and anti-tTG IgA in 64 patients with vitiligo and 64 controls; each group included 41 (64.1%) women and 23 (35.9%) men. Among the patients with vitiligo, autoantibody tests were positive in two (3.1%) women. No one in the control group has positive results for autoantibodies[16]. However, the other cross-sectional study investigated the incidence of CD in 198 patients with vitiligo and found no positive CD serology in any of the participants[20].

CD and incidence of vitiligo
The incidence of vitiligo among CD patients was examined in six cross-sectional studies and one population-based cohort study. Ertekin et al.[18] reported on 140 children with CD, of whom 3 (2.1%) had vitiligo[18], while Lancasterm-Smith et al.[26] found that 1 (1.8%) out of 57 patients with CD had vitiligo[26]. Further, Seyhan et al.[19] studied 55 cases of children and adolescents with CD and found that 45 children (81.8%) had gastrointestinal symptoms; 5 of them were subsequently diagnosed with vitiligo, with an incidence rate of 9.1%[19]. A Swedish population-based cohort study, in which each CD patient was matched with five control patients, demonstrated that among 43300 patients with CD, 106 cases (0.2%) were affected by vitiligo. Moreover, in a population of 198532 patients, vitiligo was diagnosed in 261 cases (0.1%), and the incidence of vitiligo was statistically significant[27]. In a study in Italy, 1 of 82 patients with CD had vitiligo (incidence rate of 1.2%)[28]; another report including 1010 patients with CD in Spain found that only 4 children (0.4%) had vitiligo[29]. However, surprisingly, Reunala et al.[30] did not report the onset of vitiligo in 383 patients with CD who received GFD[30]. GFD may reduce the risk of vitiligo.

GFD and vitiligo
Only a few cases of GFD and vitiligo have been reported in the literature. Our literature review identified two case reports describing the recoloring of vitiligo lesions after the onset of a GFD. One case reported a 9-year-old child with both CD and vitiligo who developed extensive repigmentation after following a GFD for 1 year[21]. The second report describes a 22-year-old female patient with vitiligo, who received a 2-year treatment including dapsone with no significant response but began to recover after 1 mo of GFD[31]. These cases suggest that elimination of gluten in the early stages of disease may have the potential to encourage and improve the disease.

Additionally, there are some reports on the coexistence of DH and vitiligo. Two case reports describe this relationship: in both, the DH lesions were significantly improved after the patients began a GFD; however, the vitiligo lesions remained unchanged or further aggravated. One report described a 53-year-old woman with vitiligo and DH. The patient began a GFD, and DH was completely relieved after 5 mo, but vitiligo did not subside and further increased[32]; she did not undergo a CD-related examination. The second case report described a 21-year-old patient with vitiligo and DH who was
Table 1 Summary of studies reporting prevalence of celiac disease in vitiligo

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Country</th>
<th>Study design</th>
<th>Setting</th>
<th>Vitiligo, n (%)</th>
<th>CD prevalence (V + CD)</th>
<th>Vitiligo diagnosis</th>
<th>CD diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shahmoradi et al[16], 2013</td>
<td>Iran</td>
<td>Case-control study</td>
<td>Hospital</td>
<td>64</td>
<td>3.1% (n = 2)</td>
<td>Medical records</td>
<td>Serology</td>
</tr>
<tr>
<td>Volta et al[20], 1997</td>
<td>Italy</td>
<td>Cross-sectional study</td>
<td>Hospital</td>
<td>198</td>
<td>0</td>
<td>NA</td>
<td>Serology and histology</td>
</tr>
<tr>
<td>Henker and Hartmann[24], 2019</td>
<td>Germany</td>
<td>Cross-sectional study</td>
<td>Hospital</td>
<td>176</td>
<td>2.8% (n = 5)</td>
<td>Medical records</td>
<td>Serology and histology</td>
</tr>
<tr>
<td>Seyhan et al[25], 2011</td>
<td>Turkey</td>
<td>Case-control study</td>
<td>Hospital</td>
<td>61</td>
<td>3.2% (n = 2)</td>
<td>NA</td>
<td>Serology and histology</td>
</tr>
</tbody>
</table>

CD: Celiac disease; NA: Not applicable.

Table 2 Summary of studies reporting prevalence of vitiligo in celiac disease

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Country</th>
<th>Study design</th>
<th>Setting</th>
<th>CD, n (%)</th>
<th>Vitiligo prevalence (V + CD)</th>
<th>Vitiligo diagnosis</th>
<th>Celiac disease diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reunala et al[30], 1997</td>
<td>Finland</td>
<td>Cross-sectional study</td>
<td>Hospital</td>
<td>383</td>
<td>0</td>
<td>Medical records</td>
<td>Histology</td>
</tr>
<tr>
<td>Ertekin et al[18], 2009</td>
<td>Turkey</td>
<td>Cross-sectional study</td>
<td>Hospital</td>
<td>140</td>
<td>2.1% (n = 3)</td>
<td>Medical records</td>
<td>Serology and histology</td>
</tr>
<tr>
<td>Lancaster-Smith et al[26], 1974</td>
<td>United Kingdom</td>
<td>Cross-sectional study</td>
<td>Hospital</td>
<td>57</td>
<td>1.8% (n = 1)</td>
<td>Medical records</td>
<td>Serology and histology</td>
</tr>
<tr>
<td>Seyhan et al[19], 2007</td>
<td>Turkey</td>
<td>Cross-sectional study</td>
<td>Hospital</td>
<td>55</td>
<td>9.1% (n = 5)</td>
<td>Medical records</td>
<td>Serology and histology</td>
</tr>
<tr>
<td>Lebwohl et al[27], 2020</td>
<td>Sweden</td>
<td>Population-Based cohort study</td>
<td>Database</td>
<td>43300</td>
<td>0.24% (n = 106)</td>
<td>Medical records</td>
<td>Histology</td>
</tr>
<tr>
<td>Catassi et al[28], 1996</td>
<td>Italy</td>
<td>Cross-sectional study</td>
<td>School</td>
<td>82</td>
<td>1.2% (n = 1)</td>
<td>Questionnaire survey</td>
<td>Serology and histology</td>
</tr>
<tr>
<td>Polanco[29], 2008</td>
<td>Spain</td>
<td>Cross-sectional study</td>
<td>Hospital</td>
<td>1010</td>
<td>0.4% (n = 4)</td>
<td>Medical records</td>
<td>Serology and histology</td>
</tr>
</tbody>
</table>

CD: Celiac disease; V: Vitiligo.

Table 3 Summary of the effect of gluten-free diet on vitiligo

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Country</th>
<th>Evidence type</th>
<th>Celiac disease diagnosis</th>
<th>Accompanied diseases</th>
<th>Measure of improvement</th>
<th>Time to dermatologic improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez-Garcia et al[31], 2011</td>
<td>Spain</td>
<td>Case report</td>
<td>Diagnosis, method not described</td>
<td>None</td>
<td>Repigmentation of skin lesions</td>
<td>1 yr, continuous improvement for 3 yr</td>
</tr>
<tr>
<td>Khandalavala et al[31], 2014</td>
<td>United States</td>
<td>Case report</td>
<td>Serology and histology not done</td>
<td>None</td>
<td>Repigmentation of skin lesions</td>
<td>1 mo, continuous improvement for 3 mo</td>
</tr>
<tr>
<td>Amato et al[32], 2000</td>
<td>Italy</td>
<td>Case report</td>
<td>Serology</td>
<td>Dermatitis herpetiform</td>
<td>No response</td>
<td>NA</td>
</tr>
<tr>
<td>Karabudak et al[33], 2007</td>
<td>Turkey</td>
<td>Case report</td>
<td>Histology</td>
<td>Dermatitis herpetiform</td>
<td>No response</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA: Not applicable

diagnosed with CD after gastrointestinal endoscopy. He was prescribed strict GFD and topical steroids, after which DH significantly improved, although his vitiligo remained unchanged[33].
Discussion of CD

CD is a chronic autoimmune disease caused by improper absorption of wheat gluten and related cereal peptides by the small intestine, and this causes the human body to lose its ability to absorb nutrients through the villi. The disease may affect patients of any age, with a peak in early childhood and the 4th and 5th decade[34]. The gastrointestinal symptoms of CD include abdominal distension, abdominal pain, chronic diarrhea, steatosis, anorexia, weight loss, and nutritional deficiency. Further, an increasing number of related diseases and parenteral manifestations have been reported[35]. Vitiligo is also associated with a variety of gastrointestinal comorbidities, including autoimmune liver disease, autoimmune atrophic gastritis, inflammatory bowel disease, and intestinal flora dysfunction[13,36-38]. Furthermore, the incidence of some autoimmune diseases (pernicious anemia, inflammatory bowel disease, systemic lupus erythematosus, Addison’s disease, and autoimmune thyroid disease) in patients with vitiligo is significantly increased[39]. These associations indicate that vitiligo has a common genetic etiology with other autoimmune diseases. Studies have found that patients with multiple autoimmune syndromes may have CD and/or vitiligo. In addition to well-defined polygenic syndromes, there may be a positive correlation between CD and vitiligo[40].

There is no published research explaining the pathophysiological relationship between CD and vitiligo; both are T cell-mediated disorders in which gamma-delta T cells, T-helper 1, and T-helper 17 play important roles[41-44]. CD has been found to be highly correlated with interleukin (IL)-2, IL-6, IL-17, and IL-21[45-47] which have been proven to play important roles in the pathogenesis of vitiligo[48,49]. The shared immunogenic mechanisms between the two conditions could explain their association. The incidence rate of autoimmune diseases is increased in patients with prolonged gluten exposure, due to the intestinal barrier dysfunction associated with CD and increased permeability to immunogenic triggers[50]. CD patients exposed to gliadin can show triggering of the CD4 + T cell responses, causing the production of high levels of interferon-gamma; this has been related to the severity of psoriasis[51,52]. A similar mechanism may be involved in the pathogenesis of vitiligo. On the other hand, in vitiligo, nuclear factor-erythroid 2-related factor 2 activation decreased in keratinocytes with impaired phosphoinositide 3-kinase phosphorylation, increasing the susceptibility to reactive oxygen species (ROS), leading to chemically induced apoptosis[53]. Moreover, IL-15 and CD4 + T cytokines (TNF, IL-2, IL-21) increased the phosphorylation of activators of transcription (STAT) 5 and protein kinase b, as well as the transcription of B-cell lymphoma-extra-large (BCL-xL) protein. Further, TNF, IL-2, and IL-21 synergistically trigger the proliferation of Lin(-) intraepithelial lymphocytes (IELs) and CD3-CD56 + IELs in duodenal biopsy specimens of refractory CD type II (RCDII), while CD4 + T cytokines are involved in its pathogenesis[54]. Additionally, another possible mechanism linking vitiligo and CD is vitamin D deficiency in CD patients due to intestinal malabsorption[55]. Vitamin D deficiency can make susceptible individuals develop vitiligo[56]. However, this mechanism may not be important as it has been previously reported that patients with vitiligo have significant recoloring after a GFD. Large population-based studies in the future may provide better insight into the role of GFD in vitiligo.

Furthermore, CD is closely related to DH. Sulfasalazine, a commonly used treatment for DH, may induce vitiligo in patients with CD and DH[57] as it can consume glutathione, leading to a large amount of ROS accumulation, resulting in melanocyte damage[58,59]. Further, sulfasalazine is an inhibitor of the thioredoxin pathway[60], and reduced thioredoxin participates in the inhibition of tyrosinase, which is the rate-limiting enzyme in melanin biosynthesis and inhibits melanogenesis [61,62]. Moreover, sulfasalazine may reduce the level of cofactor tetrahydrobipterin (BH4) by inhibiting the squid reductase that plays a crucial role in melanin production [63]; BH4 can also lead to the production of ROS, leading to the disruption of melanin biosynthesis[64].

CONCLUSION

The analysis based on a review of existing evidence supports the association between CD and vitiligo. In the treatment of vitiligo patients, this information is particularly important because the intestinal symptoms are usually non-specific and are often ignored by doctors and patients. Further, patients with vitiligo may benefit from CD screening, while early diagnosis of vitiligo in CD patients may be beneficial because GFD may improve both conditions. However, large-scale, long-term follow-up studies...
are needed to further endorse these findings.

REFERENCES


Ecevit ÇÖ. Interleukin-6 and Interleukin-17 gene polymorphisms and celiac disease susceptibility.
Radic Biol Med 2017; 64: 62


Role of immune escape in different digestive tumours

Xin-Zhu Du, Bin Wen, Lin Liu, Ying-Ting Wei, Kui Zhao

ORCID number: Xin-Zhu Du 0000-0003-0459-5024; Bin Wen 0000-0001-8413-0037; Lin Liu 0000-0001-7246-591X; Ying-Ting Wei 0000-0001-9434-7600; Kui Zhao 0000-0002-1639-0918.

Author contributions: Du XZ performed the literature search and wrote the manuscript; Wen B categorized the information; Liu L proofread the manuscript; Wei YT checked the information; and Zhao K revised the manuscript.

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

Country/Territory of origin: China

Specialty type: Immunology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution

Abstract

A counterbalance between immune cells and tumour cells is key to fighting tumours, and immune escape is an important mechanism for the survival of tumour cells in the body. Tumor cells and their cytokines impair the activity of T cells, NK cells, macrophages and other immune cells through various ways, and change the expression of their own surface antigens so as to avoid the clearance of the immune system. Changes in major histocompatibility complex molecules, high expression of programmed death-ligand 1, and the presence of immunosuppressive cells in the tumor microenvironment (TME) are main means by which tumors impair the function of immune cells. During the development of tumours of the digestive system, different mechanisms acting on tumour cells, the TME, and immune cells lead to immune escape and promote tumour progression. In this paper, the mechanisms of immune escape in tumour cells of the digestive system are reviewed to provide a theoretical basis for the immunotherapy of gastrointestinal tumours.

Key Words: Gastrointestinal tumors; Immune escape; Immune cells; Tumor microenvironment; Molecular; Mechanism

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: To summarize and analyze the mechanisms of immune escape of tumor cells in the digestive system and provide help for immunotherapy. In this paper, the mechanisms can be analyzed from many aspects, including not only tumor cells themselves, but also immune cells and some other external factors. Through the summary of these mechanisms, we find some deficiencies in the research in this area, which may provide some ideas for the follow-up research.

Citation: Du XZ, Wen B, Liu L, Wei YT, Zhao K. Role of immune escape in different digestive tumours. World J Clin Cases 2021; 9(34): 10438-10450
INTRODUCTION

Digestive tumours are diseases with a high incidence worldwide, and the pathogenesis, clinical manifestations, and treatment of these tumours have been studied extensively. However, despite increased awareness and early screening for digestive tumours, only a few patients with distant metastases, such as colorectal cancer (CRC)[1], have long-term survival; CRC has the third-highest incidence of common tumours in the world and is the fourth leading cause of tumour-related death worldwide[2]. Therefore, it is particularly important to treat digestive tumours based on the root causes or pathogenesis. In recent years, many pieces of evidence have been obtained that support the view that the immune system plays an important role in tumorigenesis. Evading the surveillance of the immune system is also considered one of the markers of tumours. Some scholars believe that cancer immune editing includes three consecutive stages: Elimination, balance, and escape[3]. During the transformation of adenomas into malignant tumours, adenomatous dysplasia may represent an equilibrium phase, and malignant tumours may occur in the escape phase. Tumour cells escape attack from the immune system mainly by changing biological characteristics and microenvironments. Additionally, external factors can participate in immune escape. The mechanisms by which digestive tumours evade immune attack are summarized below (see Table 1).

ALTERATIONS IN MAJOR HISTOCOMPATIBILITY COMPLEX MOLECULES INVOLVED IN IMMUNE ESCAPE

Major histocompatibility complex (MHC) is a protein complex loaded with short peptides on the cell surface that can be recognized by the T-cell receptor (TCR)[3,4]. Research shows that MHC-I molecules play an important role in the acquired immune response of vertebrates and the occurrence and development of digestive system tumours[5]. For example, HLA-G, a nonclassical MHC-class I molecule, has been demonstrated to be expressed in digestive system tumours[6]. HLA-G expression was first identified at the maternal-foetal interface of cytrophoblast cells and was subsequently discovered to be involved in organ transplantation, malignant transformation, and autoimmune diseases, while allowing tumours or viruses to evade immune responses[7]. HLA-G exerts an inhibitory effect on NK cells, T lymphocytes, and antigen-presenting cells mainly by directly binding to the inhibitory receptors ILT-2, ILT-4, and KIR2DL4[8]. In addition, soluble HLA-G (sHLA-G) binds to CD8 helper receptors, leading to apoptosis of NK and T cells and weakening host immune defences[9].

Unlike HLA-G, which participates in immune escape by affecting immune cell function (mainly NK and T cells), HLA-I, a classical MHC molecule, downregulates its expression in tumour cells and reduces the expression of tumour-associated antigen (TAA) on the surface of tumour cells, thus evading recognition and attack by immune cells[10]. This process is one of the mechanisms by which oesophageal malignant tumour cells escape immune surveillance of CD8+ T cells[11]. For example, aflatoxin G1 precisely reduces the expression of immunoproteasome LMP-2 in oesophageal malignant tumour cells, and the resulting downregulation of HLA-I expression on the surface of tumour cells hinders the recognition of T lymphocytes and enables tumour cells to escape immune surveillance[12]. Downregulation or complete suppression of the HLA-I gene leads to inefficient antigen presentation and a decrease in the recognition rate of cytotoxic T lymphocytes (CTLs)[13], which suggests that the deletion of HLA-I molecules may be one of the advantages of the host evasion of immune defence. In studies on gastric malignancies associated with the Epstein-Barr virus (EBV) infection, it was found that microRNA encoded by EBV decreased the antigen presentation function of MHC-I molecules, thus enabling cells infected with EBV to escape the killing effect of immune cells[14]. MHC-II levels have also been found to be significantly higher in almost all EBV-related gastric malignancies than in normal tissues, unlike MHC-I levels[15]. This result suggests that the upregulation of the MHC-II molecule may also be involved in immune escape. The expression of HLA-
<table>
<thead>
<tr>
<th>Molecules/cells</th>
<th>Ref.</th>
<th>Tumor/cancer</th>
<th>Cells/cytokines</th>
<th>Up/down</th>
<th>Pathway/target</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-G</td>
<td>Bespalova et al [8], 2020; Liu et al. [16], 2020</td>
<td>CRC</td>
<td>NK cells, T lymphocytes, and antigen-presenting cells</td>
<td>Up</td>
<td>ILT-2, ILT-4, and KIR2DL4</td>
<td>By directly binding to the inhibitory receptors ILT-2, ILT-4, and KIR2DL4, leading to apoptosis of NK and T cells and weakening host immune defences</td>
</tr>
<tr>
<td>HLA-I</td>
<td>Zhao et al [11], 2011; Li et al. [1], 2010; Özgül Özdemir et al [19], 2016</td>
<td>Oesophageal malignant tumour, CRC</td>
<td>CD8+ T cells, T lymphocytes</td>
<td>Down</td>
<td>TAA</td>
<td>Downregulates the expression of HLA-I and reduces the expression of tumour-associated antigen (TAA) on the surface of tumour cells, evading recognition and attack by immune cells</td>
</tr>
<tr>
<td>HLA-E</td>
<td>Huang et al [17], 2017; Abd Hamid et al. [18], 2019</td>
<td>Early CRC</td>
<td>CTLs and NK cells</td>
<td>Up</td>
<td>CD94/NKG2A</td>
<td>HLA-E is overexpressed on the surface of early CRC cells and can bind to the HLA-E receptor CD94/NKG2A, which is expressed on the surface of CTLs and NK cells, thus inhibiting their activity</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Calderaro et al [27], 2016</td>
<td>Oesophageal carcinoma</td>
<td>EGFR</td>
<td>Up</td>
<td>PI3K/AKT, EGFR-RAS-RAP-ERK</td>
<td>Binding of the transmembrane protein - programmed death-ligand 1 (PD-L1) expressed in tumour cells or cells in the TME to PD-1 expressed on T cells can induce the production of immunosuppressive signals and decrease the proliferation of T cells, resulting in the depletion of T cells</td>
</tr>
<tr>
<td></td>
<td>Liu et al. [30], 2020</td>
<td>CRC</td>
<td>CCL5</td>
<td>Up</td>
<td>p65/STAT3-CSN5-PD-L1</td>
<td>Stabilizes PD-L1 in and out of cells through the p65/STAT3-CSN5-PD-L1 pathway mediated by NF-κB1 p65 (p65), which inhibits T-cell-mediated killing of HT29 tumour cells</td>
</tr>
<tr>
<td></td>
<td>Ghedini et al [31], 2018</td>
<td>CRC</td>
<td>FGFR2</td>
<td>Up</td>
<td>JAK/STAT3</td>
<td>The tyrosine kinase domain initiates a series of intracellular signal cascade reactions, activates the JAK/STAT3 signalling pathway, and induces PD-L1 expression in CRC cells, thus participating in the occurrence and development of CRC</td>
</tr>
<tr>
<td></td>
<td>Li et al. [34], 2019</td>
<td>CRC</td>
<td>CXCL5</td>
<td>Up</td>
<td>PIK3/Akt</td>
<td>The binding of CXCL5 to CXC2R on the surface of CRC cells promotes the movement of the CXCL5-CXC2R axis, thus activating the PIK3/Akt signalling pathway and upregulating the expression of PD-L1 in CRC</td>
</tr>
<tr>
<td></td>
<td>Li et al. [38], 2019</td>
<td>Gallbladder malignant tumour</td>
<td>T cells</td>
<td>Up</td>
<td>PIK3/Akt</td>
<td>Upregulation of PD-L1 in gallbladder malignant tumour cells, activated the PIK3/Akt pathway, inhibited the cytotoxicity mediated by normal T cells, and promoted tumour growth and development</td>
</tr>
<tr>
<td>Galectin-9</td>
<td>Wang et al. [41], 2016; Halama et al. [43], 2011</td>
<td>Oesophageal carcinoma, CRC</td>
<td>NK cells</td>
<td>Down</td>
<td>Rho/ROCK-1, F-actin polarization</td>
<td>The low expression of Galectin-9 may lead to decreased activation or insufficient transport of NK cells to the tumour site</td>
</tr>
<tr>
<td>DKK2</td>
<td>Xiao et al. [44], 2018</td>
<td>CRC</td>
<td>NK cells, CD8+ T cells</td>
<td>Up</td>
<td>STAT</td>
<td>The binding of DKK2 to LRPS on the surface of NK cells leads to the disordering of STAT5 nuclear localization in NK cells and hinders the activation of NK cells</td>
</tr>
<tr>
<td>MDSCs</td>
<td>Geiger et al. [53], 2016</td>
<td>CRC</td>
<td>T cells</td>
<td>Up</td>
<td>L-arginine</td>
<td>The high expression of MDSCs consumes a large quantity of L-arginine, and the resulting depletion of L-arginine affects T-cell proliferation</td>
</tr>
<tr>
<td></td>
<td>Li et al. [54], 2018</td>
<td>Oesophageal carcinoma</td>
<td>T cells</td>
<td>Up</td>
<td>Akt1/rela/IL8</td>
<td>Oesophageal malignant tumour cells can guide MDSCs to migrate to the tumour site and promote tumour progression by activating the Akt1/rela/IL8 signalling pathway</td>
</tr>
<tr>
<td>Treg cells</td>
<td>Chen et al. [60], 2017</td>
<td>CRC</td>
<td>TCR</td>
<td>Up</td>
<td>CXCL13-CXCR5 axis</td>
<td>HDCC mainly promotes the infiltration of Treg cells by binding to CXCR5 on the surface of Treg cells by secreting CXCL13,</td>
</tr>
</tbody>
</table>
CD47 can prevent macrophage-mediated immune escape of tumour cells by affecting the transcription of effector T cells at the cellular transcriptional level. NF-κB inhibits GZMB transcription in T cells, induces CTL dysfunction, and promotes tumour immune escape. NF-κB realizes the immune escape of tumour cells by affecting the transcription of effector T cells at the cellular transcriptional level. NF-κB inhibits GZMB transcription in T cells, induces CTL dysfunction, and promotes tumour immune escape.

CD47 can prevent macrophage-mediated phagocytosis and antigen presentation by interacting with the receptor Sirp α expressed on macrophages, thus allowing tumour cells to escape the immune surveillance of macrophages.

IDO facilitates immune escape by locally increasing the level of canine uric acid derived from tumour epithelial cells and consuming tryptophan. The increased level of canine uric acid promotes the differentiation of Treg cells through the aromatic hydrocarbon receptor AhR, and the depletion of tryptophan can lead to cell cycle arrest of T cells, both of which can inhibit the antitumour immune response.

G in CRC cells is associated with high tumour grades and poor prognosis[16]. In addition to HLA-G, the upregulation of another nonclassical MHC molecule, HLA-E, in CRC has also been confirmed to participate in immune escape. In contrast to HLA-G, HLA-E is primarily involved in the immunosuppressive response to early CRC[17]. HLA-E is overexpressed on the surface of early CRC cells and can bind to the HLA-E receptor CD94/NKG2A, which is expressed on the surface of CTLs and NK cells, thus inhibiting their activity[18]. Additionally, HLA-E expression can inhibit cetuximab-mediated antibody cytotoxicity and promote the immune escape of CRC[19]. Both nonclassical and classical MHC molecules, such as HLA-I, are expressed on CRC cells. Prognostic studies of patients with CRC suggest a poor overall survival rate in patients with deletion or downregulation of HLA-I[20]. This result supports the hypothesis that HLA-I is involved in immune escape. In a study on gastric cancer, patients with loss of expression of MHC-I molecules on the surface of tumour cells had shorter overall survival than those with normally expressed MHC-I molecules[21]. In pancreatic malignancies, tumour cells actively degrade MHC-I through the autophagy-lysosomal system, resulting in an MHC-I deficiency and providing favourable conditions for immune escape[22]. The alteration of MHC molecules has been found to significantly affect the immunogenicity of many gastrointestinal tumour cells. However, there is little evidence to support that changes in MHC molecules are involved in the immune escape of liver tumours, and further investigation is required to determine whether MHC molecules are involved in the tumour progression.

**CYTOKINES INVOLVED IN IMMUNE ESCAPE**

Tumor microenvironment (TME) consists of an extracellular matrix and mesenchymal cells, which produce cytokines that play an intermediary role in promoting tumour progression[23,24]. Binding of the transmembrane protein - programmed death-ligand 1 (PD-L1) expressed in tumour cells or cells in the TME to programmed death 1 (PD-1) expressed on T cells can induce the production of immunosuppressive signals and decrease the proliferation of T cells, resulting in the depletion of T cells. This binding process is one of the most important mechanisms of immune escape of tumour cells in the digestive system[25-27].

In the TME, the cytokines involved in the immune escape of tumour cells do not act directly on tumour cells but use signalling pathways to achieve PD-L1 upregulation.
involved in immune escape *via* different mechanisms. In oesophageal malignancies, the activation of an EGFR-dependent PI3K/AKT pathway upregulates PD-L1 on the surface of tumour cells. In addition to the PI3K/AKT pathway, the upregulation of PD-L1 in oesophageal carcinoma is also affected by the EGFR-RAS-RAF-ERK and EGR-PLC-γ signalling pathways[28]. In gastric malignant tumour cells associated with EBV infection, the expression of PD-L1 is a common feature, and the overexpression of PD-L1 is associated with poor prognosis, but the mechanism is not clear. In addition, a significantly elevated PD-1 lymphocyte count has been found in tumour stroma[29]. Some studies have shown a significant increase in the average expression level of PD-1 on T cells in peripheral blood and cancer tissues of patients with gastric cancer, suggesting that the PD-L1/PD-1 pathway is involved in immune escape in gastric cancer. Studies have also shown that a variety of cytokines participate in the immune escape process of CRC cells. For example, CCL5, a cytokine C-motif chemokine ligand 5 (CCL5) from tumour-associated macrophages (TAMs), stabilizes PD-L1 in and out of cells through the p65/STAT3-CSN5-PD-L1 pathway mediated by NF-kB1 p65 (p65), which inhibits T-cell-mediated killing of HT29 tumour cells, which is key for CRC cells to escape immune surveillance[30]. Not only do TAMs participate in the upregulation of PD-L1, but TAM subtype M2 macrophages also participate in the upregulation of PD-1 expression, which promotes the binding of PD-L1/PD-1. In addition, in the TME, VEGF-c is a growth factor involved in tumour-associated lymphangiogenesis that can also promote M2-mediated immune escape by changing the density of TAMs, as well as increasing the percentage of M2/M1 macrophages in TAMs and the M2 survival rate. The tumour-derived fibroblast growth factor receptor (FGFR)-2 binds to ligand fibroblast growth factors (FGFs) in the tumour microenvironment and undergoes dimerization (receptor dimer pairing). The tyrosine kinase domain initiates a series of intracellular signal cascade reactions, activates the JAK/STAT3 signalling pathway, and induces PD-L1 expression in CRC cells, thus participating in the occurrence and development of CRC[31,32]. PD-L1 and FGFR2 have been found to be overexpressed in CRC and positively correlated with each other[33]. It has also been observed that the overexpression of FGFR2 in CRC not only increased the apoptosis rate of T cells but was also correlated with lymph node metastasis, clinical stage cancer, and a poor survival rate. In addition to the JAK/STAT3 signalling pathway, the PIK3/Akt pathway, which has a high activation, is also one of the means of PD-L1 upregulation, with chemokine-5 (CXCL5) from cancer-associated fibroblasts (CAFs) as the medium [34,35]. CXCL5 is an effective cytokine that affects the TME in many ways, of which the PI3K/AKT signalling pathway is the most common. The binding of CXCL5 to CXCRI on the surface of CRC cells promotes the movement of the CXCL5-CXCR2 axis, thus activating the PI3K/AKT signalling pathway and upregulating the expression of PD-L1 in CRC[36]. In liver tumour cells, the expression of PD-L1 decreases antitumour immune ability and promotes the immune escape of tumour cells[37]; PD-L1 expression has been shown to be related to the invasiveness of tumour cells[27]. It has also been observed that PD-L1 expression was upregulated in gallbladder malignant tumour cells, activated the PIK3/Akt pathway, inhibited the cytotoxicity mediated by normal T cells, and promoted tumour growth and development[38]. PD-L1 expression is higher in invasive pancreatic malignant tumours, and the non-Smad-β signalling pathway mediated by the transforming growth factor in the TME leads to more invasive phenotypes and immunosuppression mediated by PD-L1[39]. All these results confirm that PD-L1 is involved in the immune escape of digestive system tumours.

In some digestive system tumours (such as an oesophageal malignant tumour, CRC), some cytokines can also promote immune escape by affecting the function of immune cells. For example, Galectin-9 is a widely expressed protein in the TME that plays a dual role in the immune escape of tumour cells. Galectin-9 can not only affect the activity of NK cells through the signalling pathway mediated by TIM-3 (an immunosuppressive molecule) but can also bind to effector CD8+ T cells expressing TIM-3 molecules in the TME, leading to apoptosis and promoting the occurrence of antitumour immunosuppression[40]. However, Galectin-9, as a protective factor against tumours, can also increase the recruitment of NK cells by affecting the expression of Rho/ROCK-1 and F-actin polarization[41]. Most tumour cells express Galectin-9 but at a lower positive rate and expression level than in normal tissues. In a prognostic study of patients with an oesophageal malignant tumour, it was found that low expression of Galectin-9 was closely related to poor prognosis[42]. These results suggest that the low expression of Galectin-9 may lead to decreased activation or insufficient transport of NK cells to the tumour site[43], which may be a new mechanism of tumour cell immune escape. In CRC, transcriptional activator (STAT) is the key regulator of NK cell functional activation, and dckkopf-associated protein 2
(DKK2), which is exploited via the high expression of a secretory protein in CRC tissue to affect the function of NK cells. The binding of DKK2 to LRP5 on the surface of NK cells leads to the disordered localization of STAT5 in NK cells and hinders the activation of NK cells[44]. DKK2 can also block the activation of CD8+ T cells, not by direct action on T cells but by indirect regulation of CD8+ T cells after direct interaction with NK cells[45]. In addition, DKK2 can inhibit the antitumour immune response by inhibiting the activation of CD8+ T cells mediated by IL-15[46].

Some studies have shown that, in addition to programmed death ligands, apoptosis antigen 1 (Fas) is also involved in the immune escape of digestive system tumours. Fas promotes apoptosis of tumour cells, whereas Fas ligand (FasL) has a protective effect on Fas-mediated apoptosis[17]. It has been found that FasL expressed by pancreatic tumor cells can avoid immune surveillance by inducing apoptosis of infiltrating lymphocytes around tumour tissue[47], but relatively few studies on FasL have been conducted to date.

**IMMUNOSUPPRESSIVE CELLS INVOLVED IN IMMUNE ESCAPE**

There are two important immunosuppressive cells in the TME, myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Treg cells). These two types of cells function both interdependently and independently during the process of suppression of antitumour immunity by digestive system tumour cells[48-50]. As the most common immunosuppressive cells, MDSCs exert inhibitory effects, such as on the production of anti-TAA antibodies and T cells and the function of NK cells, mainly through the transforming growth factor-β[51]. However, in digestive system tumours, MDSCs participate in immune escape mainly by inhibiting T-cell proliferation[52]. An important factor related to the inhibitory effect of MDSCs on T cells is L-arginine, an amino acid essential for T-cell proliferation and normal function. The high expression of MDSCs consumes a large quantity of L-arginine, and the resulting depletion of L-arginine affects T-cell proliferation[53]. Many scholars have confirmed that MDSCs are involved in the immune escape of digestive system tumours. Studies have shown that oesophageal malignant tumour cells can guide MDSCs to migrate to the tumour site and promote tumour progression by activating the Akt1/rela/IL8 signalling pathway[54]. The immunosuppressive effect of MDSCs on T cells in gastric tumour tissue has been related to the transforming growth factor β[55], and the upregulated expression of MDSCs in liver tumour cells has been related to poor prognosis[56].

In addition to affecting T-cell function, another important role of MDSCs is to stimulate the development of another key immunosuppressive cell, Treg cells, which can indirectly inhibit the TCR-mediated immune response, leading to antitumour suppression[57-59]. The CRC process involves another cell related to Treg cells, HDCC, a myeloid cell expressing histidine decarboxylase[60]. HDCC mainly promotes the infiltration of Treg cells by binding to CXCR5 on the surface of Treg cells by secreting CXCL13, which initiates the CXCL13-CXCR5 axis, promotes the proliferation of Treg cells and the aggregation of Treg cells at the tumour site. HDCC can also affect the function of Treg cells directly or indirectly by regulating the function of CD8+ T cells and thus plays an important role in inhibiting antitumour immunity. CD70+CAFs may also play a role in immune escape by promoting the aggregation of Treg cells and increasing the migration ability of Treg cells[61].

MDSCs and Treg cells complement each other. MDSCs can induce the production of Treg cells; conversely, Treg cells can stimulate the production of MDSCs through positive feedback of the transforming growth factor-β[51]. MDSCs can not only damage the activation of T cells by producing O2 and iNOS but also cooperate with the VEGF to induce angiogenesis around tumour cells and directly stimulate tumour growth and metastasis[62-65]. In the TME, many favourable factors act as "fertile soil" for the growth of MDSCs to promote the immune escape of digestive system tumours. Factors such as PGE2, IL-6, IL-10, LTB4, and histamine are involved in the induction of MDSCs; local hypoxia and low pH in the TME can stimulate the expression of MDSCs, and S100A9 is a proinflammatory molecule that can induce an immunosuppressive microenvironment by regulating the chemotaxis and activation of MDSCs in digestive system tumours[66].
IMMUNOSUPPRESSIVE MOLECULES INVOLVED IN IMMUNE ESCAPE

Some immunosuppressive molecules in tumour cells, immune cells, and other immune-related cells, such as TIM-3, CD47, and NF-kB, play a key role in the process of immune escape of tumours.

TIM-3 is a coinhibitory receptor that can be expressed not only in immune cells (including immunosuppressive cells) and tumour cells but also in other cells. TIM-3 acts as a negative regulator in immune cells (such as CD4+ Th1 and CD8+ T cells) and thus plays an important role in T-cell depletion in a variety of environments[67], whereas TIM-3 expression is promoted in immunosuppressive cells (such as dysfunctional CD8+ T cells and FoxP3+ Treg cells, two key cells in tumour development)[68, 69]. TIM-3 is also expressed in cell types other than the two abovementioned cell types [70], including myeloid cells and digestive system tumour cells themselves. A high expression of TIM-3 in tumour cells often indicates a poor prognosis of tumours[71], and studies have shown that TIM-3 can induce metastasis of oesophageal malignant tumours through the AKT/GSK-3β/Snail signalling pathway[72]. In this regard, the TIM-3 molecule is a very suitable target for antitumour immunotherapy, and an in-depth study of TIM-3 may help identify new directions in immunotherapy.

The upregulation of CD47 expression in some digestive system tumours has been confirmed[73-75] and is closely related to the occurrence of gastric tumours associated with EBV infection[74]. CD47 can prevent macrophage-mediated phagocytosis and antigen presentation by interacting with the receptor Sirp α expressed on macrophages, thus allowing tumour cells to escape the immune surveillance of macrophages[76]. Furthermore, CD47 promotes the proliferation and metastasis of CRC cells by increasing aerobic glycolysis and activating the MAPK signalling pathway[77]. When blocking the PD-L1/PD-1 axis with an anti-PD-1 antibody, CD47/Sirp α signal transduction can be weakened[78], suggesting that there may be a common pathway between the PD-L1/PD-1 axis and CD47-mediated immune escape, which is extremely significant for the further study of anti-immunotherapy.

Another common immunosuppressive molecule, NF-kB, is widely found in tumour cells of the digestive system and participates in immune escape mainly by affecting the function of T cells. In a study on the effect of microtubule-associated serine/threonine kinase (MAST1) on gastric malignant tumours, it was found that tumour cells after MAST1 gene knockout exerted an antitumour effect by downregulating the expression of NF-kB p65, suggesting that NF-kB may be involved in the immune escape of tumour cells[79,80]. NF-kB1 p50 (hereinafter referred to as p50) realizes the immune escape of tumour cells by affecting the transcription of effector T cells at the cellular transcriptional level[81,82]. P50 is a transcriptional inhibitor of the T cell granzyme B gene (GZMB). By binding to an unknown kβ element in the GZMB promoter, p50 inhibits GZMB transcription in T cells, induces CTL dysfunction, and promotes tumour immune escape. The activation of p50 and the expression of GZMB have been found to be negatively correlated with the degree of T-cell infiltration in CRC; that is, in CRC with a high level of p50 activation, the expression of GZMB was downregulated and T-cell infiltration decreased, whereas in CRC with a low level of p50 activation, the expression of GZMB was upregulated and T-cell infiltration increased. During the development of colitis into CRC, the colitis-related immune response may first activate p50 and damage the function of CTL effectors, leading to the immune escape of transformed epithelial cells and tumour development. In addition, in gallbladder malignant tumours, the downregulated expression of miR-146b-5p increases the expression of Toll-like receptor 4 (TLR4) and indirectly activates the NF-kB signalling pathway, which regulates tumour development[83]. Tumour proliferation, epithelial transformation, and stem cell-like characteristics were found to be inhibited when the phosphorylation pathway of NF-kB/p65 was blocked in pancreatic malignant tumour cells[84], which suggests that NF-kB is involved in the development of pancreatic malignant tumours. Therefore, the activation of NF-kB is considered to be a key link in the carcinogenesis of the human digestive system[85].

OTHER PROCESSES INVOLVED IN IMMUNE ESCAPE

The interaction between tumour cells and immune cells plays an important role in the occurrence of inflammation-related tumours. The reaction between tumour cells and immune cells has two facets: CTLs activated by antitumour action inhibit tumour growth, while chronic inflammation creates a microenvironment that promotes tumour cell growth and invasion. Studies have shown that an elevated level of the...
inflammatory cytokine IL-6 can upregulate the expression of the cell adhesion molecule ICAM1 through the STAT3/5, ERK, and Rho-ROCK signalling pathways and promote the formation of chronic inflammation and lymphocyte death in tumour tissue, which enables the tumour to evade immune attack[86].

The inflammatory process induces tumour or immune cells to release cytokines[87] and is part of tumour immunosuppression, which plays an important role in tumour immune escape of the digestive system. In addition to the mechanism of the inflammatory reaction, another type of cell, the STAT1-dependent indole-2-dioxygenase-1 (IDO1) Paneth cell, plays an essential role in immune escape. In oesophageal malignant tumours, the expression of IDO has been found to impair the function of CD8+ T cells and promote the immune escape of oesophageal malignant tumours[88, 89]. IDO facilitates immune escape by locally increasing the level of canine uric acid derived from tumour epithelial cells and consuming tryptophan. The increased level of canine uric acid promotes the differentiation of Treg cells through the aromatic hydrocarbon receptor AhR29[90], and the depletion of tryptophan can lead to cell cycle arrest of T cells[91], both of which can inhibit the antitumour immune response. In addition, IDO participates in the immune escape of colitis-associated CRC, where IDO1 Paneth cells exist in both cancer tissue and normal intestinal recess[92]. IDO1 Paneth cells can be used as local immunosuppressants to prevent the abnormal activation of immune cells by bacteria and promote tumour progression.

In recent years, in-depth study of the digestive system has resulted in the identification of factors related to immune escape. For example, in a study on the relationship between intestinal flora and CRC, it was found that Clostridium could expand myeloid immune cells, inhibit the proliferation of T cells in CRC and induce T-cell apoptosis[93]. In blood circulation, platelets inhibit the immune response of T cells to CRC through the GARP-TGF-β axis; thus, drugs such as clopidogrel can improve the immunosuppressive response through antiplatelet aggregation[94]. In the TME, high levels of insulin and epidermal growth factor may be risk factors for tumour escape. When the TME is anoxic, lactic acid produced by tumour cells can weaken the differentiation and effector function of T cells and monocytes[95]. In addition, some RNAs can promote immune escape by affecting the function of immune cells. For example, microRNA-21 induces immunosuppression of CRC by increasing the levels of IL-10 and PGE2 (PGE2 inhibits DCs, macrophages, neutrophils, CTLs, TH1 cells, and NK cells and stimulates the production of MDSCs, Treg cells, and TH2)[96], and circRNA participates in the immune escape of liver tumour cells by regulating the function of NK cells[97].

CONCLUSION

The immune system is the body’s protective barrier, and immune escape is really the umbrella for tumors. The immune escape of tumour cells in the digestive system is mainly realized by changing the expression of MHC molecules through various mechanisms; affecting the function of T cells, NK cells, and other immune cells; stimulating the activation and accumulation of immunosuppressive cells; and finally promote the immune escape of tumour cells, which is the key breakthrough of tumour immunotherapy. Among carcinogenic mechanisms, the immune escape mechanism of tumour cells provides a reliable basis for the further study of immunotherapy, which is expected to become a milestone in the history of tumour treatment that goes beyond surgical treatment, radiotherapy, and chemotherapy. Existing studies have confirmed that immune escape is involved in the development of most digestive system tumors, but it has been rarely reported in liver cancer, whether the immune escape is involved in the formation of it needs further study in the future. Although the development of digestive system tumours is closely related to the immune escape mechanism, it is difficult to block tumour progression at the root using a single locking mechanism; thus, many aspects and multiple dimensions of the immune escape mechanism need to be studied in the future. In-depth exploration of various mechanisms will help lay a theoretical foundation for further progress in immunotherapy.

ACKNOWLEDGEMENTS

The authors thank Professor Tuo BG (Department of Gastroenterology, Affiliated Hospital of Zunyi Medical College) for professional assistance.
REFERENCES


**23** Arnetth B. Tumor Microenvironment. *Medicina (Kaunas)* 2019; *56* [PMID: 31906017 DOI: 10.3390/medicina56010015]


Du XZ et al. IEM in different digestive system tumours


Chen X, Takemoto Y, Deng H, Midelhoff M, Friedman RA, Chu TH, Churchill MJ, Ma Y, Nagar


Ono M. Control of regulatory T-cell differentiation and function by T-cell receptor signalling and Foxp3 transcription factor complexes. Immunology 2020; 160: 24-37 [PMID: 32022254 DOI: 10.1111/imn.13175]


Du XZ et al. IEM in different digestive system tumours
Basic Study

Magnolol protects against acute gastrointestinal injury in sepsis by down-regulating regulated on activation, normal T-cell expressed and secreted

Shi-Hao Mao, Dan-Dan Feng, Xi Wang, Yi-Hui Zhi, Shu Lei, Xi Xing, Rong-Lin Jiang, Jian-Nong Wu

ORCID number: Shi-Hao Mao 0000-0002-0060-6286; Dan-Dan Feng 0000-0002-0014-6929; Xi Wang 0000-0003-4861-0441; Yi-Hui Zhi 0000-0002-0106-2276; Shu Lei 0000-0002-0036-7879; Xi Xing 0000-0002-9491-7084; Rong-Lin Jiang 0000-0002-3821-0228; Jian-Nong Wu 0000-0001-8867-9860.

Author contributions: Mao SH, Wu JN, Feng DD and Jiang RL designed and coordinated the research study; Mao SH, Wu JN, Feng DD and Wang X performed the research; Lei S, Zhi YH and Xing X interpreted the data; Mao SH, Feng DD and Wang X analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

Institutional animal care and use committee statement: All animal experiments conformed to the internationally accepted principles for the care and use of laboratory animals (licence No. SYXK(Zhe)2013-0184).

Conflict-of-interest statement: We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any

Abstract

BACKGROUND
Sepsis is a major medical challenge. Magnolol is an active constituent of Houpu that improves tissue function and exerts strong anti-endotoxin and anti-inflammatory effects, but the mechanism by which it reduces intestinal inflammation in sepsis is yet unclear.

AIM
To assess the protective effect of magnolol on intestinal mucosal epithelial cells in sepsis and elucidate the underlying mechanisms.

METHODS
Enzyme-linked immunosorbent assay was used to measure tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and regulated on activation, normal T-cell expressed and secreted (RANTES) levels in serum and ileal tissue in animal studies. The histopathological changes of the ileal mucosa in different groups were observed under a microscope. Cell Counting Kit-8 and cell permeability assays were used to determine the concentration of drug-containing serum that did not affect the activity of Caco2 cells but inhibited lipopolysaccharide (LPS)-induced decrease in permeability. Immunofluorescence and Western blot assays were used to detect the levels of RANTES, inhibitor of nuclear factor kappa-B kinase β (IKKβ), phosphorylated IKKβ (p-IKKβ), inhibitor of nuclear factor kappa-B kinase α (IkBα), p65, and p-p65 proteins in different groups in vitro.
nature or kind in any product, service and/or company that could be construed as influencing the position presented in the manuscript entitled.

Data sharing statement: No additional data are available.

ARRIVE guidelines statement: The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

Supported by Basic Public Welfare Research Foundation of Zhejiang Province, China, No. GD21H290001; and Traditional Chinese Medicine Science and Technology Project Foundation of Zhejiang Province, China, No. 2020ZB072.

Country/Territory of origin: China

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/License s/by-nc/4.0/

Received: July 20, 2021
Peer-review started: July 20, 2021
First decision: August 9, 2021

RESULTS
In rats treated with LPS by intravenous tail injection in the presence or absence of magnolol, magnolol inhibited the expression of proinflammatory cytokines, IL-1β, IL-6, and TNF-α in a dose-dependent manner. In addition, magnolol suppressed the production of RANTES in LPS-stimulated sepsis rats. Moreover, in vitro studies suggested that magnolol inhibited the increase of p65 nucleation, thereby markedly downregulating the production of the phosphorylated form of IKKβ in LPS-treated Caco2 cells. Specifically, magnolol inhibited the translocation of the transcription factor nuclear factor-kappa B (NF-kB) from the cytosol into the nucleus and down-regulated the expression level of the chemokine RANTES in LPS-stimulated Caco2 cells.

CONCLUSION
Magnolol down-regulates RANTES levels by inhibiting the LPS/NF-kB signaling pathways, thereby suppressing IL-1β, IL-6, and TNF-α expression to alleviate the mucosal barrier dysfunction in sepsis.

Key Words: Sepsis; Magnolol; Regulated on activation, normal T-cell expressed and secreted; Anti-inflammation; Lipopolysaccharide; Nuclear factor-kappa B

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In this study, it was found that magnolol inhibited the lipopolysaccharide-induced nuclear factor-kappa B signaling pathway in the intestinal mucosal epithelium to regulate the secretion of regulated on activation, normal T-cell expressed and secreted (RANTES) and thus reduce intestinal inflammation in sepsis. Various biological constituents, isolated from traditional Chinese medicine, show multifunctional activities. Magnolol, isolated from Magnolia, has been documented to possess a range of biological activities. The current results for the first time proved that magnolol plays a role in the treatment of sepsis by down-regulating RANTES. Thus, additional studies on its anti-inflammatory mechanism might provide novel ideas and methods for the clinical prevention and treatment of sepsis.

Citation: Mao SH, Feng DD, Wang X, Zhi YH, Lei S, Xing X, Jiang RL, Wu JN. Magnolol protects against acute gastrointestinal injury in sepsis by down-regulating regulated on activation, normal T-cell expressed and secreted. World J Clin Cases 2021; 9(34): 10451-10463
URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10451.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10451

INTRODUCTION
Severe sepsis is a life-threatening syndromic response with a 27%-54.1% mortality rate [1,2]. However, the underlying mechanism is not yet understood. It is speculated that mucosal epithelial dysfunction and acute gastrointestinal injury (AGI) are the initial factors of multiple-organ failure[3], which permit translocation of intestinal bacteria and endotoxins to the bloodstream, inducing a strong systemic inflammatory response and leading to AGI[4,5]. Currently, the diagnosis of AGI is poorly understood. Border et al[6] first reported an association between bacterial translocation and gut-origin sepsis in 1987. Since then, the gut has been shown to have a major role in the progression of systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction syndrome (MODS). Several studies have reported that increased intestinal permeability in acute bowel injury results in the translocation of large amounts of intestinal bacteria, thus initiating or aggravating systemic inflammatory response syndrome[7]. The current treatment for sepsis to prevent MODS requires rapid diagnosis to allow timely treatment with antibiotics and interventions[8]. Therefore, early and effective inhibition of the production of proinflammatory factors may protect against the intestinal damage caused by excessive inflammation in addition to preventing and treating sepsis and MODS.
Houpu is a traditional Chinese medicine for phlegm and gas removal. In clinical practice, Houpu is widely utilized for treating vomiting and diarrhea, abdominal distension, and constipation. Some studies suggested that Houpu improves gastrointestinal ischemia, inhibits bacterial migration, and reduces endotoxin absorption, and could be the favored approach in adjusting immunity[9,10]. Magnolol, an active constituent of Houpu, improves tissue function, exerts strong anti-endotoxin and anti-inflammatory effects, and acts as an oxygen-free-radical scavenger[11]. However, the exact mechanism underlying the magnolol effect on intestinal inflammation is yet unclear.

A subset of CC motif chemokines and cytokines is increased in sepsis patients compared to normal controls[12]. Various interactive and dynamic chemokines involved in sepsis are used in diagnosis, prognosis, etiology, and evaluation of response to therapy[13]. Regulated on activation, normal T-cell expressed and secreted (RANTES) is a critical member of the chemokine superfamily; its specific receptor is the transmembrane G protein-coupled receptor (CCR1, CCR2, CCR3, CCR4, and CCR5). CCR1 and CCR5 are high-affinity receptors, while CCR4 is a low-affinity receptor[14]. RANTES and its receptors affect chemotaxis or stimulation of T lymphocytes, monocytes, eosinophils, and basophils, especially in lymphocyte CD4+/CD45RO+ memory type, to induce T cell activation and proliferation, regulate Th cell and cytotoxic cell immune response, and stimulate eosinophils, basophils, and degranulation[15]. Ajuebor et al[16] found that RANTES was significantly expressed in Sprague-Dawley (SD) rats with chronic colitis. The same study suggested that the administration of the receptor antagonist reduced the colon tissue damage along with the number of mononuclear cells, mast cells, and neutrophils in the lesion. Furthermore, Kucuk et al[17] treated colitis with Met-RANTES and found less damage and bacterial translocation. Previous studies have shown that the promoters of RANTES genes contain the binding sites for the transcription factor nuclear factor-kappa B (NF-kB)[18].

NF-kB is a nuclear transcription factor in cells involved in the inflammatory and immune responses of the body and regulates cell apoptosis, stress response, and NF-kB overactivation. NF-kB has been associated with several human diseases, such as rheumatoid arthritis and inflammatory changes in the heart and brain diseases. NF-kB is a major transcription factor in the inflammatory response, and its accumulation in the nucleus influences transcription by binding to the promoter of the RANTES gene, thereby inducing its production in large quantities[19]. Magnolol significantly suppresses the expression of tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), phosphorylated extracellular regulated protein kinases (p-ERK), phosphorylated C-Jun N-terminal kinase (p-JNK), and p-p38 in lipopolysaccharide (LPS)-induced mouse uterine epithelial cells (MUECs), which is associated with the inhibition of Toll-like receptor 4 (TLR4)-regulated NF-kB signaling[20]. Therefore, whether magnolol can inhibit the LPS/NF-kB signaling pathway in the intestinal mucosal epithelium to regulate the secretion of RANTES and thus reduce intestinal inflammation in sepsis needs to be further investigated.

MATERIALS AND METHODS

Animals

All animal studies (including mouse euthanasia) were carried out in compliance with the regulations and guidelines of Zhejiang Chinese Medical University institutional animal care and according to the Institutional Animal Care and Use Committee (IACUC) guidelines. Healthy male SD rats (n = 55), weighing 200 ± 20 g, were obtained from the Experimental Animal Center of Zhejiang Chinese Medical University, China (certification number SCXK [Hu] 2017-0005) and housed for 2 wk under normal conditions (certification number SYXK [Zhe] 2013-0184) at 20 ± 1 °C and 50%-60% humidity, under 12:12-h light/dark cycle, with a ventilation rate of 8-15 times/h.

Using a random number table, the rats were divided into five groups (n = 11/group): Control group (Control), severe sepsis group (Model), low-dose magnolol (Tongtian Biologicals, Shanghai, China) group (LM, 5 μg/kg), middle-dose magnolol group (MM, 10 μg/kg), and high-dose magnolol group (HM, 20 μg/kg).

Animal model establishment and treatment

A rat model of severe sepsis was established by intravenous injection of LPS via the tail vein. Briefly, all rats were deprived of food but had free access to water for 12 h before surgery. The Control rats received 15 μg/kg normal saline plus 4 mg/kg normal
saline. The Model animals received 15 μg/kg normal saline plus 4 mg/kg LPS. The rats in the LM, MM, and HM groups received 5 μg/kg magnolol plus 4 mg/kg LPS, 10 μg/kg magnolol plus 4 mg/kg LPS, and 20 μg/kg magnolol plus 4 mg/kg of LPS, respectively. Blood was collected from each group after 6, 12, and 24 h. After 24 h, the animals were euthanized using an intraperitoneal injection of chloral hydrate, and their mesenteric lymph nodes, liver, spleen, and terminal ileum tissues were collected under aseptic conditions.

Detection of serum and ileal inflammatory reaction
TNF-α, IL-1β, and IL-6 levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Medical Equipment Co., Ltd (80-2), Shanghai, China).

Pathological changes in the ileal mucosa
The paraffin sections of the rat terminal ileum were stained with hematoxylin and eosin and observed under an XZT-302 microscope (Shanghai Yuguang Detection Equipment Co., Ltd, Shanghai, China) at ×100 magnification to assess the histopathological changes.

Expression of RANTES in serum and ileal tissue
Peripheral blood samples and serum were isolated. Serum RANTES levels were measured using ELISA kits following the manufacturer’s instructions (Shanghai Medical Equipment Co., Ltd (80-2), Shanghai, China).

Caco2 cell culture and treatment
Caco2 cells were cultured in RPMI-1640 medium containing 20% fetal bovine serum (FBS), 100 U/mL penicillin, and 100 U/mL streptomycin (Gibco, Waltham, United States). The cells were incubated (Thermo Scientific, Waltham, United States) at 5% CO₂, 37 °C, and saturated humidity. The medium was changed every 2-3 d until the cells reached 80% confluency. Under a microscope (Olympus, Tokyo, Japan), Caco2 cells were observed to be adherent like paving stones.

Subsequently, cells were divided into four groups: Group A (Solvent), treated with solvent only; group B (Magnolol), treated with different concentrations of magnolol (2 μmol/L, 5 μmol/L, and 10 μmol/L); group C (LPS), treated with solvent and LPS (100 μg/mL); group D (Magnolol plus LPS), treated with magnolol (2, 5, and 10 μmol/L) and LPS (100 μg/mL). Groups B/C/D were pretreated with magnolol or solvent for 8 h, followed by LPS for 24 h.

Cell counting kit-8 assay
After 24 h of culture, cells were digested with trypsin-EDTA (Solarbio, Beijing, China) and collected by centrifugation at 1000 rpm for 5 min (Eppendorf, Hamburg, Germany) and resuspended in complete fresh medium (GIBCO, Waltham, United States). The cell suspension was inoculated in a 96-well plate and incubated at 37 °C and 5% CO₂. Then, 10 μL of cell counting kit-8 (CCK-8) (Biyuntian, C0037, Shanghai, China) was added to each well and incubated at 37 °C for another 2 h. The absorbance was measured at 450 nm using a microplate reader (Thermo Scientific, Waltham, United States).

Cell permeability detection
Caco2 cells in the logarithmic phase were inoculated in 24-well Transwell (Corning, 3415, Shanghai, China) plate. Epithelial cells were inoculated in the upper chamber. The filtration membrane embedded in the chamber was a polycarbonate membrane, on which the cells grew to form a monolayer. After the epithelial cells were overgrown, phenol-free red minimum essential medium (MEM) (GIBCO, Waltham, United States) containing fluorescein isothiocyanate isomer (FITC)-labeled glucan (10 kDa, 100 μg/mL) (Santa Cruz, Sc-263323), magnolol, and LPS was added to the upper chamber, and phenol-free red MEM containing glucan, magnolol, and LPS was added to the lower chamber. After treatment for 12 h, 100 μL of the lower chamber medium was placed in 96-well plates, and the fluorescence intensity of FITC was detected by an enzyme marker (excitation wavelength of 490 nm and emission wavelength of 520 nm) (Thermo Scientific, Waltham, United States).

ELISA
According to the CCK-8 and cell permeability detection, we found that 10 μmol/L of magnolol had a maximal inhibitory effect on increased permeability of Caco2 cells after LPS induction. Caco2 cells were divided into four groups again and treated with
the appropriate concentrations of magnolol. RANTES levels were measured using ELISA kits, according to the manufacturer’s instructions (Shanghai Medical Equipment Co., Ltd (80-2), Shanghai, China).

**Western blot analysis**

Caco2 cells were lysed in 200 mL of radio-immunoprecipitation assay (RIPA) (Beyotime Biotechnology, Shanghai, China) buffer and homogenized. The protein concentration was determined using the bicinchoninic acid method. The cells were then washed with ice cold phosphate buffered saline (PBS) (Sinopharm Chemical Reagent, Shanghai, China) and re-centrifuged at 5500 rpm for 5 min at 4 °C. The cell pellets were re-suspended in a lysis buffer [100 mmol/L phenylmethylsulfonylfluoride (PMSF) (Aladdin, Shanghai, China), 10 μL phosphatase inhibitor (Beyotime Biotechnology, Shanghai, China)] for 30 min. The lysate was centrifuged at 12000 rpm for 5 min at 4 °C before the supernatant was collected. We performed the Bradford assay (Biorad, Hercules, CA, United States) and UV spectrophotometry (Bio-wave II; Biochrom WPA, Cambridge, United Kingdom) to equalize loading protein. Equal amounts of protein (40 μg) were transferred to vinylidene fluoride membranes (Milipore, Billerica, MA, United States). The membranes were incubated with blocking buffer [5% non-fat dry-milk in TBS containing 0.1% Tween-20 (TBST)] for 2 h at room temperature. The membranes were probed with anti-RANTES (1:2000; AF5151, Affinity Biosciences, United States), anti-IKKβ (1:2000; AF6009, Affinity Biosciences, United States), anti-p-IKKβ (1:2000; AF3010, Affinity Biosciences, United States), anti-IKBα (1:2000; AF5002, Abcam, United Kingdom), anti-p65 (1:2000; ab16502, Affinity Biosciences, United States), and anti-p-p65 (1:2000; AF2006, Affinity Biosciences, United States) polyclonal antibodies overnight at 4 °C. Subsequently, the membranes were incubated with horseradish peroxidase (HRP)-labeled goat anti-rabbit secondary antibody (1:50000, BA1054, Dr. DE Biological Engineering Co. Ltd, Wuhan, China) at 37 °C for 2 h. GAPDH (AB-P-R 001, Xianzhi Biology Co. Ltd, Hangzhou, China) was used as the internal control and detected on the membrane. The signals were detected on an X-ray imaging system (6535876, Ruike Medical Equipment Co., Ltd, Xiamen, China), and the gray value of the immunoreactive bands was analyzed using BandScan.

**Immunofluorescence**

Cells were dehydrated, cleared, waxed, embedded, sliced, and incubated with primary antibody (Abcam, United States) and secondary antibody (San Eagle, Wuhan, China). Subsequently, the cells were stained with 4,6-guanidine-2-phenyl indole (DAPI) and observed under a confocal microscope (Perkin Elmer & Olympus, Tokyo, Japan).

**Statistical analysis**

Data were analyzed using IBM SPSS Statistics version 22. Measurement data following a Gaussian distribution are expressed as the mean ± SD. The comparison between groups was conducted using the LSD method (minimum significance method) in one-way ANOVA or t-tests as appropriate. P values < 0.05 indicated statistical significance.

**RESULTS**

**Establishment of a rat model of sepsis**

During the 24-h postoperative observation period, no rats died in the Control group. Two rats each died in the Model group and the low-dose LM group, and one rat each died in the MM and the HM groups, corresponding to the death rates of 0%, 18.18%, 18.18%, 9.09%, and 9.09%, respectively, which did not differ significantly between the groups.

The rats in the Control group behaved normally, were sensitive, and had glossy hair, normal stool, and no hyperemia or edema in the intestine. Within 6 h post-intervention, the other four groups of mice exhibited a series of abnormalities, such as piloerection, shortness of breath, listlessness, loss of appetite, diarrhea, loss of interest in the surrounding environment, the disappearance of self-cleaning behavior, and increased secretion from the eyes. The symptoms of the HM, MM, and LM groups were milder compared to those of the Model group. After 12 h, the HM, MM, and LM groups showed signs of mental improvement and self-cleaning behaviors, while the Model group did not.
**Protective effects of magnolol on intestinal mucosal barrier of rats with sepsis**

Compared to the Control group, the levels of serum and ileal TNF-α, IL-1β, and IL-6 were significantly higher those of the Model group ($P < 0.01$; Tables 1 and 2), while they were decreased slightly in the LM, MM, and HM group ($P < 0.05$; Tables 1 and 2).

**Magnolol improves intestinal mucosal morphology**

In the Control group, the ileal mucosal villi were arranged in an orderly manner, and the structure of the surrounding blood vessels was normal. In the Model group, the ileal mucosal villi were damaged. The intestinal mucosal epithelial cells were degenerated and wiped off, the subepithelial capillaries exhibited dilation and congestion, and inflammatory cells were diffused in the lamina propria. Compared to the Model group, the morphology of the ileal mucosal villi in the three magnolol groups was improved, although slight damage to the ileal mucosal villi, local necrosis, and some bleeding were observed. A pronounced improvement in ileal mucosal morphology was observed in the HM group (Figure 1A-E).

**Magnolol decreases RANTES release in serum and expression in ileal tissue of sepsis rats**

Compared to the Control group, the RANTES release in serum was significantly increased in the Model group ($P < 0.05$, Table 1). Magnolol decreased the RANTES release in the LM, MM, and HM groups compared to the Model group ($P < 0.05$, Table 1). Moreover, the RANTES expression levels in ileal tissue were significantly decreased in the LM, MM, and HM groups compared to the Model group ($P < 0.05$, Table 2).

**Effects of different concentrations of magnolol on Caco2 permeability induced by LPS**

CCK-8 cells were used to detect cell permeability. The relative absorbance value of Caco2 cells treated with solvent was 1.0. No significant change was detected in cell permeability after adding different concentrations of magnolol (Figure 2). Conversely, the permeability of Caco2 cells increased significantly in the LPS-treated Caco2 cells ($P < 0.01$, Figure 2). However, compared to the LPS-treated Caco2 cells, the permeability decreased significantly when Caco2 cells were treated with magnolol before LPS treatment ($P < 0.01$, Figure 2).

**Magnolol decreases RANTES expression in Caco2 cells induced by LPS**

The RANTES expression in Caco2 cells in each group was determined by ELISA and Western blot analysis (Figure 3A and B). The expression of RANTES in Caco2 cells without LPS treatment was low, and magnolol had little effect on the expression of RANTES. On the other hand, LPS increased the level of RANTES in Caco2 cells, which was significantly inhibited by magnolol ($P < 0.01$, Figure 3A).

**Magnolol inhibits LPS-induced activation of NF-κB signaling pathway**

No significant difference was observed in the expression of inhibitor of nuclear factor kappa-B kinase (IKK) and p65 in different groups (Figure 4A). LPS increased the phosphorylated level of inhibitor of nuclear factor kappa-B kinase $\beta$ (IKK$\beta$) and p65 in Caco2 cells and decreased the expression of inhibitor of nuclear factor kappa-B kinase $\alpha$ (IkBa). Magnolol inhibited the increased phosphorylation of IKK and p65 in LPS-treated Caco2 cells and reversed the down-regulation of IkBa. Compared to the Solvent group of Caco2 cells, the p65 distribution in the nucleus of Caco2 cells treated with 10 $\mu$mol/L of magnolol did not change significantly ($P > 0.05$), while LPS enhanced the translocation of p65 to the nucleus. Compared to the LPS-treated Caco2 cells, 10 $\mu$mol/L of magnolol reduced the nuclear p65 abundance in Caco2 cells (Figure 4B).

**DISCUSSION**

The intestinal tract is the most commonly involved organ in sepsis. According to statistics, up to 60% of sepsis cases are accompanied by gastrointestinal tract dysfunction[21]. The intestinal tract is also the second-largest immune organ of the body. The gut has long been considered the “motor” of the systemic inflammatory response[22]. The common factors, TNF-α, IL-1β, IL-6, and IL-1β, are mainly secreted by activated mononuclear macrophages and partially by other nucleated cells[23]. IL-6...
Table 1 Serum regulated on activation, normal T-cell expressed and secreted, tumor necrosis factor α, interleukin 1β, and interleukin 6 levels in rats of different groups

<table>
<thead>
<tr>
<th>Group</th>
<th>RANTES (ng/mL)</th>
<th>TNF-α (pg/mL)</th>
<th>IL-1β (pg/mL)</th>
<th>IL-6 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 11)</td>
<td>0.65 ± 0.25</td>
<td>124.91 ± 11.29</td>
<td>185.87 ± 24.97</td>
<td>183.69 ± 43.02</td>
</tr>
<tr>
<td>Model (n = 9)</td>
<td>5.17 ± 0.70</td>
<td>256.89 ± 19.55</td>
<td>383.01 ± 41.85</td>
<td>380.99 ± 44.11</td>
</tr>
<tr>
<td>LM (n = 9)</td>
<td>4.07 ± 0.67</td>
<td>167.39 ± 20.92</td>
<td>318.83 ± 74.06</td>
<td>308.21 ± 73.22</td>
</tr>
<tr>
<td>MM (n = 10)</td>
<td>3.13 ± 0.45</td>
<td>143.87 ± 15.22</td>
<td>256.79 ± 25.37</td>
<td>246.14 ± 41.73</td>
</tr>
<tr>
<td>HM (n = 10)</td>
<td>2.52 ± 0.28</td>
<td>144.49 ± 18.02</td>
<td>225.07 ± 17.46</td>
<td>215.18 ± 12.49</td>
</tr>
</tbody>
</table>

The contents of regulated on activation, normal T-cell expressed and secreted and cytokines in serum of septic rats after magnolol intervention were determined using enzyme-linked immunosorbent assay. All data are represented as the mean ± SD.

*P* < 0.01 vs Control group.

*P* < 0.05 vs Model group.

*P* < 0.01 vs LM group.

*P* < 0.05 vs MM group.

**Table 2 Ileal regulated on activation, normal T-cell expressed and secreted, tumor necrosis factor α, interleukin 1β, and interleukin 6 levels in rats of different groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>RANTES (g/mL)</th>
<th>TNF-α (pg/mL)</th>
<th>IL-1β (pg/mL)</th>
<th>IL-6 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 11)</td>
<td>3.40 ± 1.45</td>
<td>347.04 ± 60.66</td>
<td>240.4 ± 37.08</td>
<td>195.11 ± 28.60</td>
</tr>
<tr>
<td>Model (n = 9)</td>
<td>29.29 ± 4.07</td>
<td>1015.7 ± 90.98</td>
<td>453.52 ± 54.82</td>
<td>436.01 ± 46.29</td>
</tr>
<tr>
<td>LM (n = 9)</td>
<td>22.47 ± 3.72</td>
<td>720.82 ± 88.16</td>
<td>330.89 ± 49.06</td>
<td>337.66 ± 73.79</td>
</tr>
<tr>
<td>MM (n = 10)</td>
<td>17.39 ± 2.59</td>
<td>487.48 ± 115.29</td>
<td>301.43 ± 44.51</td>
<td>271.25 ± 36.82</td>
</tr>
<tr>
<td>HM (n = 10)</td>
<td>14.10 ± 1.59</td>
<td>428.79 ± 48.71</td>
<td>294.27 ± 68.2</td>
<td>237.75 ± 16.05</td>
</tr>
</tbody>
</table>

The expression levels of regulated on activation, normal T-cell expressed and secreted and cytokines in ileal tissue of septic rats after magnolol intervention were determined using Western blot assay. All data are represented as the mean ± SD.

*P* < 0.01 vs Control group.

*P* < 0.05 vs Model group.

*P* < 0.01 vs LM group.

*P* < 0.05 vs MM group.

**TNF-α**: Tumor necrosis factor-α; **IL-1β**: Interleukin-1β; **IL-6**: Interleukin-6; **RANTES**: Regulated on activation, normal T-cell expressed and secreted; **Control**: The Control group; **Model**: Severe sepsis group; **LM**: Low-dose magnolol group; **MM**: Middle-dose magnolol group; **HM**: High-dose magnolol group.

is secreted by mononuclear macrophages, fibroblasts, and endothelial cells. The primary function of the intestinal tract is to promote the acute phase protein synthesis and participate in inflammation. In the hemorrhagic shock model, IL-6 gene knockout protected the rats from intestinal barrier dysfunction[24]. Therefore, IL-6 has been suggested as a common inflammatory indicator of intestinal barrier dysfunction[25]. TNF-α is mainly secreted by activated mononuclear macrophages, and its main function is to heat and dilate blood vessels, and promote the chemotactic adhesion of neutrophils[26]. In the sepsis model, the increase in serum and tissue TNF-α has been closely related to mortality[27]. TNF-α is released at the initial stage of inflammation. It promotes the secretion of IL-1β and IL-6 and also stimulates the expression of adhesion molecules on the surface of intestinal microvascular endothelial cells and neutrophils, accelerating neutrophil aggregation and releasing the reactive oxygen and proteolytic enzymes. These phenomena disrupt the intestinal mucosal epithelium and accelerate apoptosis of intestinal mucosal epithelial cells[28].

In this study, we quantitatively detected the differences in the expression levels of inflammatory factors in each group, such as IL-1β, IL-6, and TNF-α. In the severe sepsis group, the expression levels of all the three inflammatory factors were significantly increased, which were consistent with previous studies[29]. After magnolol administration, the release of inflammatory cytokines was reduced in a dose-dependent manner, and the apoptosis of LPS-induced ileal epithelial cells was
Figure 1 Hematoxylin and eosin staining of ileal tissues. A: Control group shows orderly arranged ileal mucosal villi; B: Model group shows damaged ileal mucosal villi. The epithelial cells at the villus tips were wiped off, the subepithelial capillaries exhibited congestion, the central lacteals were expanded, the lamina propria was exposed and disintegrated, and blood capillaries were bleeding, with ulcer formation and widened intracellular tight junctions; C-E: Ileal mucosal structure in rats of the LM (C), MM (D), and HM (E) groups, respectively. The morphology of ileal mucosal villi and intestinal glands was improved to varying degrees compared to panel B. The ileal mucosal morphology was improved in panel E compared to D and in D compared to C. Magnification, × 100. Control: The control group; Model: Severe sepsis group; LM: Low-dose magnolol group; MM: Middle-dose magnolol group; HM: High-dose magnolol group.

Figure 2 Effects of different concentrations of magnolol on Caco2 cell permeability induced by lipopolysaccharide. Cell permeability was evaluated to determine the concentration of magnolol that inhibited the lipopolysaccharide (LPS)-induced increased permeability of Caco2 cells. After adding LPS, the permeability of the cells was significantly increased ($P < 0.01$). After adding magnolol to LPS-treated Caco2 cells, the permeability of the cells was decreased in a dose-dependent manner ($P < 0.01$). Control: Treated with solvent only; 2 μmol/L, 5 μmol/L, and 10 μmol/L magnolol: Treated with different concentrations of magnolol; LPS: Treated with solvent and LPS (100 μg/mL); LPS + magnolol (2 μmol/L, 5 μmol/L, and 10 μmol/L): Treated with magnolol (2 μmol/L, 5 μmol/L, and 10 μmol/L) and LPS (100 μg/mL); OD520nm: Optical density at 520 nm; FITC: Fluorescein isothiocyanate isomer. LPS: Lipopolysaccharide.

pronounced. Therefore, we speculated that magnolol prevents the aggravation of inflammation and the damage of intestinal mucosal tissues.

RANTES, a member of the chemotactic cytokine CC subgroup, also known as CCL5, is secreted by epithelial cells[25,30]. RANTES plays a critical role in chemotactic and stimulating T cells, accumulating a large number of T cells in the inflammatory lesions, activating T cells to produce inflammatory factors, and aggravating the tissue damage. Several studies have shown that RANTES is highly superficial in the intestinal
Mao SH et al. Magnolol protects against AGI in sepsis

Figure 3 Expression of regulated on activation, normal T-cell expressed and secreted protein in Caco2 cells in each group. A: The cells were pretreated with magnolol or solvent for 8 h, followed by lipopolysaccharide (LPS) (100 μg/mL) for 24 h. The content of RANTES in the supernatant of the four groups of cells was determined by ELISA. Data are presented as the mean ± SD; the comparison between different groups was performed using the LSD method in one-way ANOVA (*P < 0.01); B: The cells were pretreated with magnolol or solvent for 8 h and then with LPS (100 μg/mL) for 24 h. The expression of RANTES protein in Caco2 cells in each group was detected by Western blot analysis. 0 or Solvent: Treated with solvent only; 10 μmol/L magnolol: Treated with 10 μmol/L magnolol; LPS: Treated with solvent and LPS (100 μg/mL); LPS + magnolol 10 μmol/L: Treated with magnolol 10 μmol/L and with LPS (100 μg/mL); GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; RANTES: Regulated on activation, normal T-cell expressed and secreted.

Figure 4 Nuclear factor-kappa B pathway-related protein expression and p65 nucleation in Caco2 cells in each group. A: The cells were treated with magnolol or solvent for 8 h and then with lipopolysaccharide (LPS) (100 μg/mL) for 24 h. The protein levels of phosphorylated inhibitor of nuclear factor kappa-B kinase β and p65 were assessed by Western blot; B: Fluorescence distribution of p65 in the nucleus of Caco2 cells treated with magnolol or solvent for 8 h and then with LPS (100 μg/mL) for 24 h. Control or Solvent: Treated with solvent only; 10 μmol/L magnolol: Treated with 10 μmol/L concentration of magnolol; LPS: Treated with solvent and LPS (100 μg/mL); LPS + magnolol 10 μmol/L: Treated with magnolol 10 μmol/L and with LPS (100 μg/mL); GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; DAPI: 4,6-diamidino-2-phenylindole; IKKβ: Inhibitor of nuclear factor kappa-B kinase β; p-IKKβ: Phosphorylated inhibitor of nuclear factor kappa-B kinase β; IκBα: Inhibitor of nuclear factor kappa-B kinase α; LPS: Lipopolysaccharide.

Also, its high expression is an indicator of sepsis in premature infants and neonates[32,33]. In the current study, RANTES was significantly increased in both serum and ileal tissue after LPS treatment as well as inflammatory factors. This phenomenon proved that the RANTES has a positive role in inflammation-induced LPS models. However, the serum secretion was consistent with the decreased expression of RANTES in ileal tissue after administration of magnolol, which further indicated its role in resisting the inflammatory response in sepsis.

The mechanisms by which magnolol regulates RANTES to reduce damage in intestinal mucosal epithelial cells are not well-understood. It has been hypothesized that the NF-κB signaling pathway is closely related to the production of various cytokines, chemokines, and adhesion factors in oxidative stress and inflammatory response. In normal cells, NF-κB is retained in the cytoplasm due to binding to its inhibitory protein IκB and kinase IKKα/β. When inflammation occurs, phosphorylated...
IkBs and IKKa/β may activate the NF-κB signaling pathway, thus leading to nucleation of p65 and p50 and promoting transcriptional activation of the relevant target genes[34]. When NF-κB is dislodged from the complex, it translocates rapidly from the cytoplasm to the nucleus and aggregates in the nucleus to induce RANTES by binding to its promoter[19]. Several studies have shown that patients with inflammatory bowel disease exhibit high expression of p65 in the nucleus of cells in intestinal mucosal tissue. Abnormal expression of intracellular p65 was also detected in the dextran sodium sulfate (DSS)-induced colitis model. Simultaneously, PDTC, an inhibitor of NF-κB, significantly upregulates the expression of the dense protein in DSS-induced colon cancer rats, restores the normal intestinal mucosal permeability, and reduced the inflammatory response[35]. The current results revealed that after magnolol treatment, the permeability of Caco2 cells induced by LPS, the phosphorylation of IKKβ, and the nucleation of p65 was decreased, and the expression of RANTES was down-regulated. The abnormal activation of the NF-κB signaling pathway was closely correlated with the expression of RANTES during inflammation, and magnolol inhibited the up-regulation of RANTES expression in the NF-κB signaling pathway.

We found that in our study, inhibition of serum TNF-α levels by magnolol was only partial, i.e., 50%-60% inhibition vs Model group and there may be enough circulating TNF-α for host defense. It appears that magnolol has more than a single anti-inflammatory effect in the treatment of sepsis. Some studies have reported that drugs with anti-inflammatory actions, such as antioxidative agents, could regulate immunity dysfunction with apparent safety in sepsis[36,37]. As we know, pathogen-associated molecular patterns (PAMPs) can lead to the initiation of innate immune and inflammatory responses. TLRs are a group of evolutionarily conserved and membrane-bound pattern recognition receptors that recognize various PAMPs including microbial nucleic acids, lipids, proteins, lipoproteins, and glycoproteins[38,39]. We have found that magnolol could down-regulate RANTES levels by inhibiting the TLR4-regulated NF-κB signaling pathways. Taken together, these findings suggest that magnolol may have an immunomodulating role in sepsis. We will test this idea in subsequent experiments.

CONCLUSION

Overall, magnolol significantly alleviates inflammatory response and pathological changes in the intestinal tissue and the levels of RANTES expression in rats with sepsis. The abnormal activation of the NF-κB signaling pathway is closely correlated with the expression of RANTES during inflammation, and magnolol inhibits the up-regulation of RANTES expression via the NF-κB signaling pathway. Thus, this study provided the pharmacological proof for use of magnolol and suggested that it is a potential agent in the prevention and treatment of sepsis. Further studies should be conducted to clarify the underlying mechanism(s) of the anti-inflammatory and immunomodulating role of magnolol in sepsis.

ARTICLE HIGHLIGHTS

Research background
Sepsis is a major medical challenge, and finding specific targets and effective drugs is a scientific concern. Currently, various biological constituents are isolated from traditional Chinese medicine and have been confirmed to possess multifunctional activities.

Research motivation
Magnolol is an active constituent of Houpu, which improves tissue function and exerts strong anti-endotoxin and anti-inflammatory effects. Thus, we aimed to identify the role of magnolol in the treatment of sepsis.

Research objectives
To assess the protective effect of magnolol on intestinal mucosal epithelial cells in sepsis and elucidate the underlying mechanisms.
Research methods
We carried out animal studies and cell studies in vitro, respectively. In animal studies, enzyme-linked immunosorbent assay was used to measure the differentially expressed inflammatory factors and regulated on activation, normal T-cell expressed and secreted (RANTES) levels in serum and ileal tissue. In the in vitro experiments, Cell Counting Kit-8 and cell permeability assays were employed to determine the concentration of drug-containing serum that did not affect the activity of Caco2 cells but inhibited lipopolysaccharide (LPS)-induced permeability reduction. Immunofluorescence and Western blot assays were used to detect the protein levels of RANTES, inhibitor of nuclear factor kappa-B kinase (NIK), phosphorylated IκBα (p-IκBα), inhibitor of nuclear factor kappa-B kinase α (IκBα), p65, and p-p65 in different groups.

Research results
In animal studies, magnolol inhibited the expression of proinflammatory cytokines tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), and IL-6 in a dose-dependent manner and suppressed the production of RANTES in sepsis rats. In the in vitro studies, magnolol inhibited the increase of p65 nucleation and down-regulated the production of the phosphorylated form of IκBα in LPS-treated Caco2 cells. Moreover, magnolol inhibited the translocation of the transcription factor nuclear factor-kappa B (NF-kB) from the cytosol into the nucleus and downregulated the expression level of the chemokine RANTES in LPS-stimulated Caco2 cells.

Research conclusions
Magnolol downregulates RANTES levels by inhibiting the LPS/NF-kB signaling pathway, resulting in the suppression of IL-1β, IL-6, and TNF-α expression that in turn, alleviates the mucosal barrier dysfunction in sepsis.

Research perspectives
This study, for the first time, proved that magnolol plays a role in the treatment of sepsis by down-regulating RANTES, and further studies on the anti-inflammatory mechanism might provide an in-depth insight into novel methods for the clinical prevention and treatment of sepsis.

REFERENCES

9 Sun XG, Fan Q, Wang QR. [Effect of dachengqi decoction on expressions of TLR4 and TNF-alpha in the lung and the large intestine of mice with endotoxemia]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2011; 31: 244-248 [PMID: 21425583]
Mao SH et al. Magnolol protects against AGI in sepsis


Ajuebor MN, Hogaboom CM, Kunkel SL, Proudfoot AE, Wallace JL. The chemokine RANTES is a crucial mediator of the progression from acute to chronic colitis in the rat. J Immunol 2001; 166: 552-558 [PMID: 11123536 DOI: 10.4049/jimmunol.166.1.552]


37 Ma H, Kou J, Zhu D, Yan Y, Yu B. Liu-Shen-Wan, a traditional Chinese medicine, improves survival in sepsis induced by cecal ligation and puncture via reducing TNF-alpha levels, MDA content and enhancing macrophage phagocytosis. *Int Immunopharmacol* 2006; **6**: 1355-1362 [PMID: 16782549 DOI: 10.1016/j.intimp.2006.03.003]


39 Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity* 2011; **34**: 637-650 [PMID: 21616434 DOI: 10.1016/j.immuni.2011.05.006]
### Abstract

**BACKGROUND**

Idiopathic membranous nephropathy (IMN) has a high incidence in the middle-aged and elderly population, and poses a great threat to the physical and mental health and quality of life of patients. Nephritis Rehabilitation Tablets have many potential effects, such as clearing residual toxins, tumefying the kidney and spleen, replenishing qi, and nourishing yin, and have played an important role in the treatment of a variety of kidney diseases.

**AIM**

To investigate the efficacy and safety of Nephritis Rehabilitation Tablets combined with tacrolimus in the treatment of IMN.

**METHODS**

Eighty-four patients with IMN recruited from January 2017 to September 2020 were randomly divided into a study group (n = 42) and a control group (n = 42). On the basis of routine symptomatic treatment, both groups were treated with tacrolimus, and the study group was additionally treated with Nephritis Rehabilitation Tablets. Both groups were treated for 12 wk. The therapeutic effect, the levels of renal function indexes [serum creatinine (Scr), serum albumin, and 24-h urinary protein], urinary immunoglobulin (IgG4), membrane attack complex (C5b-9), and the incidence of adverse reactions were measured before and after 12 wk of treatment.

**RESULTS**
INTRODUCTION

Idiopathic membranous nephropathy (IMN) is a common pathological type of primary nephrotic syndrome. It has a high incidence in the middle-aged and elderly population, and poses a great threat to the physical and mental health and quality of life of patients[1,2]. The incidence of IMN has continued to increase in recent years, and safe and effective treatments are of significant research interest.

Glucocorticoid therapy alone has difficulty achieving ideal effects in IMN, and comprehensive intervention combined with immunosuppressants is usually needed [3]. Cyclophosphamide is commonly used in IMN and can achieve certain therapeutic effects, but the incidence of adverse reactions is high. Tacrolimus is a new calcineurin inhibitor that can effectively improve renal function with low dose and high safety. However, the overall therapeutic effect is still different from that expected in the clinic [4-6].

Attention has been given to the adjuvant therapeutic effects of traditional Chinese medicine Nephritis Rehabilitation Tablets in recent years. Nephritis Rehabilitation Tablets have many potential effects, such as clearing residual toxins, tumefying the kidney and spleen, replenishing qi, and nourishing yin, and have played an important role in the treatment of a variety of kidney diseases. In the present study, 84 patients...
with IMN at our hospital were selected and divided into groups to explore the therapeutic value of Nephritis Rehabilitation Tablets with tacrolimus.

**MATERIALS AND METHODS**

**General data**
Eighty-four patients with IMN were recruited from our hospital from January 2017 to September 2020 and were randomly divided into a study group (n = 42) and a control group (n = 42). In the study group, there were 27 males and 15 females, the age ranged from 46 to 77 years (mean, 61.56 ± 7.11 years), the course of disease ranged from 3.5 to 41.1 mo (mean, 22.29 ± 10.32 mo), and the disease stage was stage I (n = 23) or stage II (n = 19). In the control group, there were 29 males and 13 females, the age range was 45-79 years old with an average age of 62.01 ± 6.89 years, the course of disease range was 3.2-40.6 mo with an average of 21.91 ± 11.21 mo, and the disease stage was stage I (n = 24) or stage II (n = 18). The clinical data, including sex, age, course of disease, and stage of disease, were comparable between the two groups (P > 0.05).

**Selection criteria**
The inclusion criteria were: (1) The diagnosis of IMN was confirmed by renal puncture pathological examination, and the pathological stage was I or II; (2) age less than 80 years; (3) patients who were informed of the study and signed the consent form; (4) serum creatinine (Scr) < 133 umol/L; and (5) urinary protein ≥ 4 g/24 h.

The exclusion criteria were: (1) Patients with acquired immunodeficiency syndrome, hepatitis C, hepatitis B, etc., who are unable to take immunosuppressant or hormone therapy; (2) patients with malignant tumor; (3) patients with severe infection; (4) patients with coagulation dysfunction; and (5) patients with allergic constitution or history of allergy to research drugs.

**Methods**
Both groups of patients were given routine symptomatic treatment after admission, including lipid reduction, anticoagulation, blood pressure reduction, diuresis and detumescence, and oral prednisone acetate tablets 0.5 mg/kg once a day (8 wk after treatment, the dose was reduced by 10% at an interval of 2 wk to a maintenance therapy of 10-15 mg/d). On this basis, different treatment schemes were adopted: The control group was treated with tacrolimus orally at 0.05-0.1 mg/kg/d twice a day, and blood trough concentration was maintained at 4-8 ng/L; the study group was treated with Nephritis Rehabilitation Tablets orally at 1.5 g three times a day in addition to the standard treatment of the control group. Both groups were treated for 12 wk.

**Evaluation of therapeutic effects**
After 12 wk of treatment, the therapeutic effects of the two groups were evaluate: Normalization of the levels of serum albumin and Scr and 24-h urinary protein < 0.3 g were considered as complete remission; 24-h urinary protein decreased by ≥ 50% or total < 1.0 g, normalization of serum albumin, and the increase or decrease of Scr ≤ 30% were considered as partial remission. The total effective rate was calculated as (complete remission + partial remission)/total cases × 100%[7]. The indexes of renal function (Scr, serum albumin, and 24-h urinary protein) were measured before treatment and after 12 wk of treatment. The levels of urinary immunoglobulin (IgG4) and membrane attack complex (C5b-9) in the two groups were measured before and after 12 wk of treatment. Mid-stream urine was taken and put into a clean container and stored at -20 °C for detection. The level of urinary C5b-9 was determined by enzyme-linked immunosorbent assay (ELISA), and the level of IgG4 was determined by double antibody sandwich ELISA. The incidence of adverse reactions in the two groups was measured.

**Statistical analysis**
The data were analyzed with SPSS 22.0. Continuous data are described as the mean ± SD and were compared by the t-test. Categorical data are described as frequency and constituent ratio (%) and were tested by the χ² test. A nonparametric test was used to compare the continuous data that do not meet a normal distribution. P < 0.05 indicated that the difference was statistically significant.
RESULTS

Therapeutic effects
The total effective rate of the study group (90.48%) was significantly higher than that of the control group (71.43%, \( P = 0.026\); Table 1).

Renal function indexes
Before treatment, there was no significant difference in Scr, serum albumin, or 24 h urinary protein between the study group and the control group (121.97 ± 40.36 µmol/L vs 124.55 ± 38.68 µmol/L, 24.21 ± 2.35 g/L vs 23.64 ± 2.51 g/L, 7.41 g ± 2.19 g vs 7.69 ± 2.32 g; \( P = 0.766, 0.286, \) and 0.571, respectively). After 12 wk of treatment, the quantitative levels of Scr and 24-h urinary protein in the two groups were significantly lower than those before treatment, and the level of serum albumin was significantly higher than that before treatment (\( P < 0.05\)). The levels of Scr and 24-h urinary protein in the study group (86.23 ± 21.61 µmol/L and 1.63 ± 0.59 g, respectively) were significantly lower than those in the control group (101.55 ± 23.67 g µmol/L and 2.89 ± 0.79 g; \( P = 0.003 \) and 0.000, respectively), and the level of serum albumin in the study group (36.69 ± 3.69 g/L) was significantly higher than that in the control group (31.26 ± 3.35 g/L, \( P = 0.00\); Table 2).

Urinary IgG4 and C5b-9 levels
Before treatment, there was no significant difference in urinary IgG4 or C5b-9 level between the study group (14.67 ± 2.39 µg/mmol and 83.79 ± 10.66 ng/mg, respectively) and the control group (15.13 ± 2.53 µg/mmol, and 85.65 ± 11.20 ng/mg; \( P = 0.336 \) and 0.438, respectively). After 12 wk of treatment, the levels of urinary IgG4 and C5b-9 in the two groups were lower than those before treatment, and the levels of urinary IgG4 and C5b-9 in the study group (1.45 ± 0.29 µg/mmol and 44.81 ± 9.10 ng/mg, respectively) were significantly lower than those in the control group (3.13 ± 0.71 µg/mmol and 55.37 ± 10.23 ng/mg; \( P = 0.000 \) and 0.000, respectively; Table 3).

Incidence of adverse reactions
There was no significant difference in the incidence of adverse reactions between the study group (11.90%) and the control group (7.14%, \( P = 0.710\); Table 4).

DISCUSSION

The incidence of IMN can account for more than 80% of nephrotic syndromes, and it can occur at any age. Most patients have different degrees of thrombosis and proteinuria, and 30% of patients' symptoms can be relieved by themselves. However, 50% of patients' conditions progress rapidly and can progress to end-stage kidney disease within 10 years, which is a great threat\(^8\),\(^9\). As a consequence, targeted treatment should be given quickly after the onset of IMN.

Glucocorticoids are an important therapeutic drug for IMN. However, hormone therapy alone has difficulty achieving ideal results. Relevant statistics show that the incidence of renal insufficiency in IMN patients without immunosuppressant can reach 40%. The combination of hormone and immunosuppressant therapy can effectively relieve clinical symptoms, improve renal survival, and inhibit the progression of renal insufficiency\(^10\),\(^11\). Cyclophosphamide is the most commonly used immunosuppressant in the clinic and can block the synthesis of DNA in cells to achieve immunosuppression. Combined with hormones, it can enhance hormone sensitivity and improve drug efficacy. However, the incidence of adverse events such as gonadal inhibition, liver function injury, and myelosuppression is high, resulting in significant limitations in its clinical application\(^12\). Tacrolimus is a new type of immunosuppressant that can interfere with calcium-dependent signal transduction, increase calcium influx, prevent dephosphorylation of activated T nuclear factors and transcription of inflammatory factors, and inhibit T cell proliferation. Lymphocyte aggregation is prevented in the early stage of the immune reaction and thus plays a therapeutic role\(^13\),\(^14\). In addition, the value of adjuvant therapy with traditional Chinese medicine in IMN has received widespread attention in recent years. There is no record of the name of IMN in traditional Chinese medicine, but according to its characteristics, it is classified into the categories of "edema" and "turbid urine". It is considered that the pathological mechanism of the disease lies in the deficiency of the spleen and kidney, blood stasis, damp-heat, wind evil, and water dampness. Spleen
Table 1 Comparison of therapeutic effects between the two groups, n (%)  

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>Invalid</th>
<th>Total efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>42</td>
<td>26 (61.90)</td>
<td>12 (28.57)</td>
<td>4 (9.52)</td>
<td>38 (90.48)</td>
</tr>
<tr>
<td>Control</td>
<td>42</td>
<td>16 (38.10)</td>
<td>14 (33.33)</td>
<td>12 (28.57)</td>
<td>30 (71.43)</td>
</tr>
</tbody>
</table>

χ² 4.941  
P value 0.026

Table 2 Comparison of renal function indexes between the two groups (mean ± SD)  

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>Number</th>
<th>Scr (umol/L)</th>
<th>Serum albumin (g/L)</th>
<th>24 h urinary protein quantification (g)</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>Study</td>
<td>42</td>
<td>121.97 ± 40.36</td>
<td>24.21 ± 2.35</td>
<td>7.41 ± 2.19</td>
<td>0.299</td>
<td>0.766</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>42</td>
<td>124.55 ± 38.68</td>
<td>23.64 ± 2.51</td>
<td>7.69 ± 2.32</td>
<td>1.074</td>
<td>0.286</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t</td>
<td></td>
<td></td>
<td></td>
<td>0.569</td>
</tr>
<tr>
<td>After 12 weeks of treatment</td>
<td>Study</td>
<td>42</td>
<td>86.23 ± 21.61^a</td>
<td>36.69 ± 3.71^a</td>
<td>1.63 ± 0.59^a</td>
<td>0.766</td>
<td>0.571</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>42</td>
<td>101.55 ± 23.67^a</td>
<td>31.26 ± 3.35^a</td>
<td>2.89 ± 0.79^a</td>
<td>0.286</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t</td>
<td></td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
</tbody>
</table>

^P < 0.05, before treatment vs after 12 wk of treatment.

Table 3 Comparison of urinary IgG4 and C5b-9 levels between the two groups (mean ± SD)  

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>Number</th>
<th>IgG4 (ug/mmol)</th>
<th>C5b-9 (ng/mg)</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>Study</td>
<td>42</td>
<td>14.67 ± 2.39</td>
<td>83.79 ± 10.66</td>
<td>0.968</td>
<td>0.336</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>42</td>
<td>15.19 ± 2.53</td>
<td>85.65 ± 11.20</td>
<td>0.968</td>
<td>0.780</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t</td>
<td></td>
<td></td>
<td>0.438</td>
</tr>
<tr>
<td>After 12 weeks of treatment</td>
<td>Study</td>
<td>42</td>
<td>1.45 ± 0.29^a</td>
<td>44.81 ± 9.39^a</td>
<td>3.098</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>42</td>
<td>3.13 ± 0.71^a</td>
<td>55.37 ± 10.23^a</td>
<td>14.196</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t</td>
<td></td>
<td></td>
<td>4.928</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P value</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
</tbody>
</table>

^P < 0.05, before treatment vs after 12 wk of treatment.

deficiency can lead to deficiency of qi and blood, and retention of damp turbidity leads to edema. Kidney deficiency can cause nontransformation of qi and water, such as edema and kidney loss and storage, to form proteinuria[15]. Combined with the above etiology and pathogenesis, on the basis of routine intervention such as tacrolimus, Nephritis Rehabilitation Tablets were used to treat patients with IMN at our hospital. The results showed that the total effective rate of the study group was higher than that of the control group, the quantitative levels of Scr and 24-h urinary protein of the study group were lower than those of the control group, and the level of serum albumin was higher than that of the control group. This showed that the combination of tacrolimus and Nephritis Rehabilitation Tablets has more significant advantages in improving the renal function of patients with IMN, which is helpful for improving the overall therapeutic effect on the disease. The main reason is that the main components of Nephritis Rehabilitation Tablets include *Salvia miltiorrhiza*, *Ginseng*, *Hedyotis diffuse*, *Motherwort*, and *Eucommia ulmoides*, which have many effects, such as dispelling dampness and removing blood stasis, diuresis, and detumescence; tonifying qi and
nourishing yin; and tonifying the kidney and detoxification. In addition, *Motherwort*, *Salvia miltiorrhiza*, and *Hedyotis diffusa* have many effects, such as anti-erythrocyte and anti-platelet aggregation, which can reduce blood viscosity, increase renal blood flow, and prevent thrombosis[16,17]. In addition, Nephritis Rehabilitation Tablets can reduce capillary permeability, regulate microcirculation and lipid metabolism, reduce swelling and diuresis, relieve urinary protein, enhance immunity, and improve renal function. In addition, some studies have demonstrated that Nephritis Rehabilitation Tablets can repair glomerular podocytes and reduce the expression of transforming growth factor beta 1 and α-smooth muscle actin in the renal interstitium. In addition, it can maintain the filtration barrier, improve the precipitation of extracellular matrix components such as laminin and fibronectin, and regulate immune function and renal function. Moreover, it can increase liver albumin synthesis, increase plasma protein levels, and antagonize glucocorticoid-induced adverse reactions[18].

In addition, urinary IgG4 can reflect renal IgG4 deposition and is closely related to IMN disease activity. Moreover, studies have shown that IMN autoantibodies play an intermediary role, while complement proteins play an important role in organ-specific autoimmune diseases. Podocyte antigens can bind to antibodies to form subepithelial *in situ* immune complexes, and complement activation can produce C5b-9. As a consequence, the condition, therapeutic effect, and prognosis of IMN can be evaluated by monitoring the levels of urinary IgG4 and C5b-9[19,20]. The levels of urinary IgG4 and C5b-9 in the study group were lower than those in the control group (*P* < 0.05), which further confirmed that Nephritis Rehabilitation Tablets combined with tacrolimus had high therapeutic value in IMN, which could reduce the contents of urinary IgG4 and C5b-9 and improve the therapeutic effect of the disease. In addition, from the results of this study, it can be concluded that there was no significant difference in the incidence of adverse reactions between the two groups, indicating that the combination of Nephritis Rehabilitation Tablets and tacrolimus can not only achieve a good therapeutic effect but also have a satisfactory safety profile.

**CONCLUSION**

Generally, Nephritis Rehabilitation Tablets combined with tacrolimus in the treatment of IMN can effectively improve the renal function of patients and downregulate the expression of urinary IgG4 and C5b-9 on the basis of routine intervention. In addition, they can help to improve the overall treatment effect while not increasing the risk of adverse reactions. However, since this study had fewer samples, further multi-center research is required to confirm our findings.

**ARTICLE HIGHLIGHTS**

**Research background**

Idiopathic membranous nephropathy (IMN) has a high incidence in the middle-aged and elderly population, and poses a great threat to the physical and mental health and quality of life of patients. The incidence of IMN has continued to increase in recent years, and safe and effective treatments are of significant research interest.

**Research motivation**

Glucocorticoid therapy alone has difficulty achieving ideal effects in IMN, and the incidence of adverse reactions is high. Tacrolimus is a new calcineurin inhibitor that can effectively improve renal function with low dose and high safety.
Research objectives
This study aimed to investigate the efficacy and safety of Nephritis Rehabilitation Tablets combined with tacrolimus in the treatment of IMN.

Research methods
On the basis of routine symptomatic treatment, the control group was treated with tacrolimus, and the study group was treated with nephritis rehabilitation tablets in addition to control group treatment. Both groups were treated for 12 wk. The therapeutic effect, the levels of renal function indexes, and the incidence of adverse reactions were measured before and after 12 wk of treatment.

Research results
The results showed that the total effective rate of the study group was higher than that of the control group, the quantitative levels of Scr and 24-h urinary protein of the study group were lower than those of the control group, and the level of serum albumin was higher than that of the control group. IMN autoantibodies play an intermediary role, while complement proteins play an important role in organ-specific autoimmune diseases. The levels of urinary IgG4 and C5b-9 in the study group were lower than those in the control group.

Research conclusions
Nephritis Rehabilitation Tablets combined with tacrolimus in the treatment of IMN can effectively improve the renal function of patients and downregulate the expression of urinary IgG4 and C5b-9. In addition, they can improve the overall therapeutic effect while not increasing the risk of adverse reactions.

Research perspectives
This study has fewer samples, and further multi-center research is required to confirm our findings.

REFERENCES


Retrospective Cohort Study

Lamb’s tripe extract and vitamin B₁₂ capsule plus celecoxib reverses intestinal metaplasia and atrophy: A retrospective cohort study

Si-Ran Wu, Jie Liu, Li-Feng Zhang, Na Wang, Lu-Yao Zhang, Qiong Wu, Jun-Ye Liu, Yong-Quan Shi

ORCID number: Si-Ran Wu 0000-0002-4378-0794; Jie Liu 0000-0002-3869-0858; Li-Feng Zhang 0000-0001-5001-1400; Na Wang 0000-0003-0799-2681; Lu-Yao Zhang 0000-0001-9408-9496; Qiong Wu 0000-0002-3968-509X; Jun-Ye Liu 0000-0003-3616-7817; Yong-Quan Shi 0000-0001-9515-7577.

Author contributions: Wu SR, Liu J, Shi YQ, Wu Q, and Liu JY designed the research; Wu SR, Liu J, Zhang LF, and Zhang LY made up the methodology; Liu J, Zhang LF, Zhang LY, and Wang N performed the research; Wu SR, Liu J, Zhang LF, and Wu Q managed the data; Liu J, Wu Q, Liu JY, and Wang N acquired the funding; Wu SR and Liu J finished the original draft; Shi YQ, Liu JY, and Wu Q reviewed and edited the paper.

Institutional review board statement: This study was performed in accordance with the ethical principles for medical research as outlined in the Declaration of Helsinki. The study was approved by the institutional research ethics committee of the First Affiliated Hospital, the Air Force Medical University (KY20212048-C-1).

Informed consent statement: According to the approval of the institutional research ethics

Abstract

BACKGROUND

Chronic atrophic gastritis (AG) with intestinal metaplasia (IM) significantly increases the risk of gastric cancer. Some medicines have showed definite therapeutic effects in AG and IM regression.

AIM

To validate the efficacy of Lamb’s tripe extract and vitamin B₁₂ capsule (LTEVB₁₂) initial therapy and celecoxib rescue therapy for IM and AG.

METHODS

A total of 255 patients were included to receive LTEVB₁₂ initial therapy (2 capsules each time, three times daily for 6 mo) in hospital in this study. The patients with failure of IM regression continued to receive celecoxib rescue therapy (200 mg, once daily for 6 mo). After each therapy finished, the patients underwent endoscopy and biopsy examination. The regression efficiency was assessed by the operative link on gastritis assessment (OLGA) and the operative link on the gastric intestinal metaplasia assessment (OLGIM) staging system. Logistic regression analysis was applied to identify factors associated with the curative effect.

RESULTS

For LTEVB₁₂ initial therapy, the reversal rates of IM and AG were 52.95% and
INTRODUCTION

Gastric cancer (GC), one of the most common malignant tumors, has a high incidence around the world[1]. In China, GC ranks second in both the morbidity and mortality of malignant tumors. According to previous reports in 2015, approximately 498000 Chinese people died from GC per year[2]. The Correa model revealed a successive stepwise development of premalignant gastric lesions, which resulted in GC, especially for the intestinal type[3]. From decades of research, intestinal metaplasia (IM) and severe atrophic gastritis (AG) have proved to form the backdrop of dysplasia and intestinal-type gastric adenocarcinoma, so that they were considered high risk factors for GC occurrence[4,5]. Even in the low GC risk population cohort, IM and AG obtained 6.2 and 4.5 hazard ratios, respectively, compared with the normal group[6]. The view of the point of no return among gastric precancerous lesions was revealed at the end of the last century[7,8]. There were some meta-analyses supporting this view. They suggested that Helicobacter pylori eradication did not reverse IM but did have an effect on chronic AG[8-10]. However, there was still some evidence that did not support this conclusion. Some studies supported that H. pylori eradication actually could reverse the IM in the long-term follow-up, which has made the debate about the point of no return among gastric precancerous lesions persisting[11-13].

There are still some studies that found the IM reversal effect of medicine. In recent years, there have also been many reports related to drugs, including Western medicine and traditional Chinese medicine, that could reverse IM. Lamb’s tripe extract and vitamin B12 capsule plus celecoxib reverses intestinal metaplasia and atrophy: A retrospective cohort study. World J Clin Cases 2021; 9(34):10472-10483


URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10472.htm

DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10472

CONCLUSION

Monotherapy could reverse IM and AG. LTEVB12 initial therapy and celecoxib rescue therapy significantly increase the regression effect. IM may not be the point of no return among gastric precancerous lesions.

Key Words: Atrophy gastritis; Intestinal metaplasia; Celecoxib; Stomach neoplasms; Operative link on the gastritis assessment staging systems to assess IM and atrophic gastritis regression of individual lesions. Monotherapy with either Lamb’s tripe extract and vitamin B12 capsule or celecoxib could reverse IM and AG. Additionally, the results proved that the integrative therapy combining Chinese and Western medicine had better regression effects. Last but not least, the results counter the argument that IM may not be the point of no return about gastric mucosal lesions.

Core Tip: First, we used the operative link on the gastritis assessment staging systems to assess IM and atrophic gastritis regression of individual lesions. Monotherapy with either Lamb’s tripe extract and vitamin B12 capsule or celecoxib could reverse IM and AG. Additionally, the results proved that the integrative therapy combining Chinese and Western medicine had better regression effects. Last but not least, the results counter the argument that IM may not be the point of no return about gastric mucosal lesions.

Supported by Shaanxi Foundation for Innovation Team of Science and Technology, No. 2018TD-003; and Project from State Key Laboratory of Cancer Biology, No. 2019CBSKL2019ZZ07.

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

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.

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

Data sharing statement: No additional data are available.

Key Words: Atrophy gastritis; Intestinal metaplasia; Celecoxib; Stomach neoplasms; Operative link on the gastritis assessment staging systems to assess IM and atrophic gastritis regression of individual lesions. Monotherapy with either Lamb’s tripe extract and vitamin B12 capsule or celecoxib could reverse IM and AG. Additionally, the results proved that the integrative therapy combining Chinese and Western medicine had better regression effects. Last but not least, the results counter the argument that IM may not be the point of no return about gastric mucosal lesions.
Wu SR et al. LTEVβ12 plus celecoxib reverses IM

Received: March 27, 2021  
Peer-review started: March 27, 2021  
First decision: August 18, 2021  
Revised: August 31, 2021  
Accepted: October 24, 2021  
Article in press: October 24, 2021  
Published online: December 6, 2021  
P-Reviewer: Wakatsuki T  
S-Editor: Fan JR  
L-Editor: Wang TQ  
P-Editor: Fan JR

vitamin B12 capsule (LTEVβ12) is the combination of the lamb sheep’s fourth tripe extracted at low temperature, vitamin B12, and excipients. The extract of lamb’s fourth tripe contains many active substances, such as renin, pepsin, mucin, and bifidus factor. It has been proven to promote the growth and propagation of bifidobacteria in vitro [14]. Recently, many studies have shown that both the application of LTEVβ12 alone or in combination with other medication could reverse IM and AG [15,16]. Moreover, our recent study found that the use of LTEVβ12 alone for 6 mo and 12 mo reversed IM. Among all related studies, the IM regression rate of LTEVβ12 alone was reported to be up to 55.71% [16].

Cyclooxygenase-2 (COX-2), an enzyme that acts as a catalyst in the transformation of arachidonic acid into prostaglandins, has been found to participate in H. pylori-associated gastric carcinogenesis [17]. COX-2 is overexpressed in gastric carcinoma and premalignant lesions [18,19]. A selective COX-2 inhibitor, celecoxib, can observeably decrease the risk of colon, lung, breast, and prostate cancers [20]. Many studies have shown that both long-term and short-term applications of celecoxib can reverse IM and AG and even other gastric premalignant lesions [21-25]. However, these studies reported that the reversal rate of IM was approximately 40%.

On the basis of such evidence, monotherapy with either LTEVβ12 or celecoxib did not show an ideal efficiency with regard to IM regression. We conducted a retrospective cohort study to assess whether LTEVβ12 or celecoxib rescue therapy can prevent progression or enhance the regression of IM and AG.

MATERIALS AND METHODS

Patients and study design

From October 2016 to July 2019, 345 patients diagnosed with IM with or without low-grade intraepithelial neoplasia (LGIN) by upper gastrointestinal endoscopy and histopathological biopsy were enrolled and followed at the Department of Gastroenterology, Xijing Hospital, Air Force Military Medical University. The inclusion criteria were: (1) Patients aged from 18 to 75 years old; (2) IM patients with or without LGIN diagnosed by upper gastrointestinal endoscopy and histopathological biopsy; and (3) Patients without H. pylori infection confirmed by 13C-urea breath test (UBT) or patients with H. pylori infection who completed the bismuth-containing quadruple program and had confirmed successful eradication by 13C-UBT. The exclusion criteria were: (1) Previously diagnosed malignant tumor; (2) History of stomach surgery; (3) Breastfeeding or pregnancy; (4) Hypothyroidism, adrenal insufficiency, systemic lupus erythematosus, ankylosing spondylitis, and other endocrine diseases or autoimmune diseases; (5) Severe mental illness; (6) Refusal of drug treatment; (7) Diagnosis of GC or high grade intraepithelial neoplasia (HGIN) by upper gastrointestinal endoscopy and pathological examination; and (8) Severe liver and kidney dysfunction. The general situation, eating habits, behavioral characteristics (smoking and drinking), disease history, medication history, and other data of the patients were collected at the inception of the study. When the therapy was accomplished, they underwent upper gastrointestinal endoscopy and histopathological biopsy. This study was performed in accordance with the ethical principles for medical research as outlined in the Declaration of Helsinki. The study was approved by the institutional research ethics committee of the First Affiliated Hospital, the Air Force Medical University (KY20212048-C-1).

The participants received LTEVβ12 initial treatment (2 capsules each time, three times daily; GMP, the Xinjiang Uygur Autonomous Region, China) for 6 mo at first. Some participants with IM regression failure in initial therapy could choose to continue the next rescue therapy or not. The patients deciding to accept it received celecoxib rescue therapy (200 mg, once daily; Pfizer, New York, NY, United States) for 6 mo. This study is a retrospective cohort study. We determined whether the patients needed to accept celecoxib rescue therapy depending on the change of the operative link on the gastric intestinal metaplasia assessment (OLGIM) stage score before and after treatment. The study size was decided by comparing with similar studies.

Endoscopy and histological assessment

Participants with a prior diagnosis of IM and dysplasia accepted upper gastrointestinal endoscopy surveillance with a standard video endoscope (Olympus GIF-Q160, Tokyo, Japan). Comprehensive biopsy samples for histological examination were obtained from five standardized sites: Two from the antrum, two from the corpus (one from the lesser curvature and one from the greater curvature), and one
from the angulus. In the case of endoscopically visible lesions, additional targeted biopsy samples were obtained.

Three pathologists blinded to the patient clinical information independently reviewed the histology of the collected samples. The grades of IM and AG were classified according to the updated Sydney system, which scored as 0 (absent), 1 (mild), 2 (moderate), or 3 (marked). Dysplasia was assessed based on the revised Vienna classification[26,27]. Of antrum and angulus biopsy samples, the severer one was on behalf of the distal antrum mucosa score. The same method applied to corpus greater and lesser curvature biopsy samples for the corpus mucosa score. According to the standardized sites, the AG, IM, and inflammation stages in all five biopsy specimens were evaluated on the basis of the operative link on gastritis assessment (OLGA) staging system[28] and the OLGIM staging system[29]. Combining the antrum and corpus scores for AG, IM, and inflammation resulted in OLGA and OLGIM staging scores (range: 0-4, respectively). For an inconsistent diagnosis, the final decision was depended on the majority diagnosis: At least two of three pathologists agreed.

**End points and statistical analysis**

The hypothesis tested in this study was that LTEVB_{12} initial treatment and celecoxib rescue therapy could promote the reversal of IM and AG. The main observation indexes were OLGIM and OLGA stage changes. To evaluate the effects of the therapies, each subject was assigned a stage score before the therapy (A) and at the end point (B) according to OLGIM and OLGA stages. We choose to use the result of B-A to verdict the development status of gastric mucosal lesions. If B-A was > 1, = 0, and < 0, the subject was considered as progression, no-change, and regression, respectively. Regression was deemed to be effective; the others were clarified to be ineffective.

Data were analyzed with SPSS 26.0 software. Continuous variables are described as medians and interquartile ranges. Count variables are described as numbers and percentages. Comparison of the effective rate between different therapies and different OLGA and OLGIM stages was evaluated by the chi-square test or Fisher exact method. Comparison of the proportion among different OLGA and OLGIM stages before and after treatment was evaluated by rank sum test. The influence of the various factors on the efficacy was computed by univariate and multivariate logistic regression analyses with P values, odd ratios (ORs), and 95% confidence interval (CIs).

**RESULTS**

**Subject characteristics and related histology before treatment**

There were 338 IM patients consecutively enrolled in this study during a total follow-up period of 34 mo (median, 15 mo). Eighty-three patients (20 who did not complete the treatment and 63 who refused endoscopic follow-up) in the LTEVB_{12} initial therapy group and 56 (17 who did not complete the treatment and 39 who refused endoscopic follow-up) in the celecoxib rescue therapy group dropped out of the study (Figure 1). A total of 255 patients finished LTEVB_{12} initial treatment. For 120 patients, treatment was viewed as ineffective (IM regression failure). Finally, 64 patients completed rescue therapy, 28 of whom were invalid (Figure 1). For the patients receiving LTEVB_{12} and celecoxib therapy, the demographic parameters, pretreatment histological features, and baseline data are shown in the supplementary materials (Supplementary Table 1).

Before LTEVB_{12} initial treatment, the OLGIM stages in 255 patients from I to IV were 64, 110, 62, and 19, respectively, and the OLGA stages from 0 to IV were 23, 14, 102, 81, and 35, respectively. Twenty-one had LGIN at baseline. Before celecoxib rescue therapy, the OLGIM stages from I to IV in 64 patients were 6, 32, 16, and 10, and the OLGA stages from 0 to IV were 1, 0, 20, 23, and 20, respectively. One had LGIN.

**Intention-to-treat and per-protocol analysis of IM and AG regression following the two therapies**

There were 255 cases in the LTEVB_{12} initial therapy group and 64 cases in the celecoxib rescue therapy group that were enrolled for per-protocol (PP) analysis. The rates of IM and AG regression at 6 mo according to intention-to-treat (ITT) or PP analysis are shown in Table 1. The results of comparing the same patients before and after the therapies by OLGA and OLGIM stages were significantly different (for the two therapies and both stages, P < 0.01). For the LTEVB_{12} initial therapy group, about half
Table 1 Intestinal metaplasia and atrophic gastritis regression based on intention-to-treat and per-protocol analyses

<table>
<thead>
<tr>
<th>Group</th>
<th>IM regression (%)</th>
<th>AG regression (%)</th>
<th>IM or AG regression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITT analysis</td>
<td>PP analysis</td>
<td>ITT analysis</td>
</tr>
<tr>
<td>LTEVB_{12} initial therapy</td>
<td>39.94</td>
<td>52.95</td>
<td>36.39</td>
</tr>
<tr>
<td>Celecoxib rescue therapy</td>
<td>30.00</td>
<td>56.25</td>
<td>27.50</td>
</tr>
<tr>
<td>Complete therapy</td>
<td>50.59</td>
<td>85.93</td>
<td>-</td>
</tr>
</tbody>
</table>

AG: Atrophic gastritis; IM: Intestinal metaplasia; LTEVB_{12}: Lamb’s tripe extract and vitamin B_{12} capsule; ITT: Intention-to-treat; PP: Per-protocol.

Changes in OLGA and OLGIM stages before and after treatment and therapeutic efficiency among different OLGA and OLGIM stages

Figure 2 shows the proportions of patients who had IM and achieved improvement of IM after 6 mo of LTEVB_{12} and celecoxib therapy. For LTEVB_{12}, 11.76% (30/255) and 16.08% (41/255) of patients had complete disappearance of IM and AG, respectively. A total of 41.18% (105/255) and 31.16% (82/255) of patients were found to have decreased OLGIM and OLGA stages, respectively. Similarly, the rates of complete IM and AG disappearance were 6.25% (4/64) and 14.06% (9/64), respectively, following celecoxib rescue therapy. Fifty percent (32/64) and 37.5% (24/64) of patients were found to have decreased OLGIM and OLGA stages, respectively.

Depending on the OLGA and OLGIM stages, the proportions of different stages showed significant differences before and after therapies (for the two therapies and
Wu SR et al. LTEVB₁₂ plus celecoxib reverses IM

Figure 2 Proportions of intestinal metaplasia and atrophic gastritis changes after Lamb’s tripe extract and vitamin B₁₂ capsule initial therapy and celecoxib rescue therapy. L: Lamb’s tripe extract and vitamin B₁₂ capsule initial therapy; C: Celecoxib rescue therapy; OLGA: Operative link on gastritis assessment; OLGIM: Operative link on the gastric intestinal metaplasia assessment.

both stages, \( P < 0.01 \). Figure 3 shows the different OLGA and OLGIM stages changing after each therapy. The proportion of high stages was decreased by therapies. The proportion of low stages, by contrast, obviously increased. In OLGIM stages III and IV, which were viewed as a high risk for GC, the IM regression rates were all above 70% for each therapy. LTEVB₁₂ initial therapy reversed IM in 89.47% of OLGIM stage IV patients. For high-risk OLGA stages III and IV patients, the AG regression rate ranged from 50% to 100%.

In different OLGA and OLGIM stages of IM patients, therapeutic efficiency showed a significant difference in each group (Table 2). For LTEVB₁₂ therapy, patients with OLGIM or OLGA stage IV disease had higher IM and AG regression rates than those with stages I and II disease (IM: 89.5% vs 17.2% and 57.3%; AG: 100% vs 33.3% and 40.6%; \( P < 0.05 \)). For celecoxib therapy, both IM and AG regression rates showed significant differences between high stages (III and IV) and stage II (IM: 71.6% and 71.4% vs 31.4%; AG: 76.2%, 50% vs 30%; \( P < 0.05 \)). In summary, each therapy had more efficiency for patients with high OLGA or OLGIM stages.

Analysis of factors associated with curative effect

The influencing factors of two therapies were assessed by univariate and multivariate logistic regression analyses. Many factors were included in the analysis, such as sex, age, body mass index, family history of GC, smoking and alcohol status, disease history, medication history, and eating habits. The results of univariate logistic regression analysis are shown in the supplementary materials (Supplementary Tables 2 and 3). After univariate logistic regression analysis, as shown in Table 3, some factors were included in the multivariate analysis according to the inclusion criteria (\( P < 0.10 \)). Eating habits, fresh vegetable intake, and high-salt diet were viewed as independent factors for the IM reversal effect of LTEVB₁₂ therapy, especially high-salt diet. Nearly twice as many patients with a high-salt diet as those without a high-salt diet benefited from LTEVB₁₂ therapy in IM regression (OR = 1.852, 95%CI: 1.044-3.285). For AG regression, patients with low education levels (OR = 0.480, 95%CI: 0.255-0.903) may benefit more from LTEVB₁₂ therapy than patients with high education levels (\( P < 0.05 \)). For celecoxib therapy, income level (≥ 5000 yuan/mo) was the independent influencing factor for the IM regression, which suggested that celecoxib therapy for IM regression may be more effective in patients with high income levels (\( P < 0.10 \)). In addition, for male patients with LTEVB₁₂ therapy, the inflammation score (score > 2) before therapy (OR = 0.448, 95%CI: 0.223-0.898) at baseline and fresh fruit intake (OR = 2.784, 95%CI: 1.131-6.852) were associated with the effect (\( P < 0.05 \)).

DISCUSSION

Through this study, we found that both LTEVB₁₂ and celecoxib monotherapies could reverse IM and AG, and the addition of celecoxib rescue therapy to LTEVB₁₂ initial therapy further increased the regression rate of IM. After LTEVB₁₂ initial therapy and celecoxib rescue therapy, the regression rate of IM depending on the OLGIM stage was up to 85.93%. These results suggested that this complete therapy could be applied in the clinical setting to reverse precancerous lesions, especially IM.
Table 2 Intestinal metaplasia and atrophic gastritis regression rates of different operative link on gastritis assessment and operative link on gastric intestinal metaplasia assessment stages for each therapy group

<table>
<thead>
<tr>
<th>Group</th>
<th>IM regression (%)</th>
<th>AG regression (%)</th>
<th>P value</th>
<th>IM regression (%)</th>
<th>AG regression (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I stage</td>
<td>II stage</td>
<td>III stage</td>
<td>IV stage</td>
<td>I stage</td>
<td>II stage</td>
</tr>
<tr>
<td>LTEVB&lt;sub&gt;12&lt;/sub&gt;</td>
<td>17.19</td>
<td>57.27&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70.97&lt;sup&gt;b&lt;/sup&gt;</td>
<td>89.47&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt; 0.001</td>
<td>33.33</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>57.14</td>
<td>31.37</td>
<td>71.60&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71.43&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05 vs control (IM regression of stage I in LTEVB<sub>12</sub> group).
<sup>b</sup>P < 0.05 vs control (IM regression of stage II in LTEVB<sub>12</sub> group).
<sup>c</sup>P < 0.05 vs control (AG regression of stage I in LTEVB<sub>12</sub> group).
<sup>d</sup>P < 0.05 vs control (AG regression of stage II in LTEVB<sub>12</sub> group).

AG: Atrophic gastritis; IM: Intestinal metaplasia; ITT: Intention-to-treat; LTEVB<sub>12</sub>: Lamb’s tripe extract and vitamin B<sub>12</sub> capsule; OLGA: Operative link on gastritis assessment; OLGIM: Operative link on the gastric intestinal metaplasia assessment.

Table 3 Factors associated with regression of intestinal metaplasia and atrophic gastritis (multivariate analysis)

<table>
<thead>
<tr>
<th>Regression effect</th>
<th>Factor</th>
<th>LTEVB&lt;sub&gt;12&lt;/sub&gt;</th>
<th></th>
<th></th>
<th></th>
<th>Celecoxib</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR</td>
<td>95%CI</td>
<td>P value</td>
<td>OR</td>
<td>95%CI</td>
<td>P value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IM</td>
<td>Fresh vegetable intake (&gt; 100 g/d)</td>
<td>0.497</td>
<td>0.224-1.105</td>
<td>0.087</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High salt diet</td>
<td>1.852</td>
<td>1.044-3.285</td>
<td>0.035</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tea intake (&gt;100g/d)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.955</td>
<td>0.736-7.158</td>
<td>0.152</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Education level (≥ senior high school)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.672</td>
<td>0.495-5.643</td>
<td>0.408</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Income level (≥ 5000 yuan/mo)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.097</td>
<td>0.902-10.638</td>
<td>0.073</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG</td>
<td>Education level (≥ senior high school)</td>
<td>0.480</td>
<td>0.255-0.903</td>
<td>0.023</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tea intake (&gt;100g/d)</td>
<td>0.678</td>
<td>0.388-1.185</td>
<td>0.173</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Profession (ref: Farmer)</td>
<td>0.784</td>
<td>0.313-1.965</td>
<td>0.603</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Officer</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.169</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medic</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.197</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Teacher</td>
<td>1.897</td>
<td>0.620-5.804</td>
<td>0.262</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Merchant</td>
<td>1.028</td>
<td>0.361-2.933</td>
<td>0.958</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Technical staff</td>
<td>3.305</td>
<td>1.275-8.565</td>
<td>0.014</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Retired</td>
<td>1.878</td>
<td>0.791-4.458</td>
<td>0.153</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unemployed</td>
<td>1.570</td>
<td>0.612-4.027</td>
<td>0.348</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood type (ref: A)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.123</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.021</td>
<td>0.240-17.033</td>
<td>0.518</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.322</td>
<td>0.064-1.617</td>
<td>0.169</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.118</td>
<td>0.010-1.460</td>
<td>0.096</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.389</td>
<td>0.128-1.182</td>
<td>0.096</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AG: Atrophic gastritis; CI: Confidence interval; IM: Intestinal metaplasia; ITT: Intention-to-treat; LTEVB<sub>12</sub>: Lamb Tripe Extract and Vitamin B<sub>12</sub> Capsule; OR: Odds ratio; PP: Per-protocol.

LTEVB<sub>12</sub> is a kind of traditional Chinese medicine extract. Several studies have shown that it has an effect on IM and AG<sup>15,16</sup>. In addition, it was effective for clinical symptoms such as abdominal distension and lack of appetite, with an effective rate up to 91%. In contrast with studies that evaluated IM regression after 6 mo or 12
Figure 3 Changes of the different operative link on gastritis assessment and operative link on gastric intestinal metaplasia assessment stages after each therapy. L: Lamb’s tripe extract and vitamin B12 capsule initial therapy; C: Celecoxib rescue therapy; OLGA: Operative link on gastritis assessment; OLGIM: Operative link on the gastric intestinal metaplasia assessment.

mo of LTEVB12 treatment, the effective rates were 56.25% vs 55.71% and 32.9% and 41.8%, respectively. In other studies, few adverse effect or toxic side effects was found during the treatments[14-16]. The participants in our research did not show severe adverse effect and toxic side effects. Some studies have indicated that the application of aspirin or other non-steroidal anti-inflammatory drugs could restrain the development of GC[30,31]. Several studies have reported the effect of celecoxib on IM regression. COX-2 was suggested to cause H. pylori-related gastric lesions though various mechanisms. Overexpression of COX-2 and the prostaglandin cascade induced by H. pylori-induced inflammation during carcinogenesis could lead to cell proliferation, mutagenesis, mitogenesis, and inhibition of apoptosis. As a COX-2 inhibitor, celecoxib could restrain the processes as mentioned above so that it may inhibit the development of GC[17,20]. Moreover, nuclear factor kappa B activation, which acts as a major mediator of H. pylori-related inflammation, was reported to be inhibited by celecoxib[32,33]. Wong et al[25] reported that the combination of anti-H. pylori therapy and celecoxib did not show better effects than anti-H. pylori therapy alone. However, two studies found that after eradication therapy (1 year and 3 years apart), celecoxib still had an effect on IM and AG regression[21,22]. This might contribute to the persistent existence of the tumor microenvironment even after H. pylori eradication[34,35]. In contrast with other studies that evaluated IM regression after 12 mo or 2 mo of celecoxib treatment, the rate was 56.25% vs 42% and 51.3% and 28.6%, respectively. It was also significantly different even when compared with the nondrug group (16.1% and 20.0%)[21-23].

The complete therapy used traditional Chinese medicine extract and Western medicine in turn, which could combine the advantage of both sides. In Taipei consensus on integrative traditional Chinese and Western medicine, Western medicine was deemed to play a part in the disease diagnosis and therapy, yet was still not perfect with deficiency. Traditional Chinese medicine had complementary and alternative effect which is indispensable[36]. A meta-analysis indicated that traditional Chinese medicine is more effective than current routine pharmacotherapy in clinical symptom relief, H. pylori eradication, and efficacy under endoscopy[37]. Thus, LTEVB12 initial therapy and celecoxib rescue therapy actually enhance the regression rate of gastric mucosal lesions with few adverse effects and toxic side effects.

Generally, the effective rate of each monotherapy for IM in our study was better or at least not inferior to that in other studies. Following the complete therapy, the IM regression rate was up to 85.93%, obviously improving the efficacy of IM regression. In addition, in contrast to previous studies, we had a larger sample in this study. Moreover, in our study, we chose the OLGIM and OGLA stages to assess the effect of IM and AG regression. Some studies chose other methods, such as the mean IM score (MIM), to assess the IM and AG regression effects[24]. MIM was the sum of all IM scores from all samples divided by the number of tissues, which led to the assessment of the effect of regression by lesions, not patients. Compared with other evaluation methodologies of histological examination, OLGA and OLGIM stages exhibited superior capability to assess the individuals. OLGA and OLGIM stages combines the location and degree of gastric mucosal atrophy and IM, which could better reflect the severity of gastric mucosal lesions. What’s more, the OLGA and OLGIM stages have been applied to evaluate the risk of GC in the clinic, which could be much more
Wu SR et al. LTEVB₁₂ plus celecoxib reverses IM

persuasive[38,39]. In each monotherapy in this study, high GC risk patients with OLGIM or OLG stages III and IV disease had good effects compared with low-risk patients with low stage disease. Kang et al[40] conducted a 3-year follow-up study in Korea and found that the severe grade of IM was associated with the improvement of IM in the body (OR = 5.14; P < 0.05). This result may be attributed to some reasons. Patients with high OLGIM or OLG stage usually had more serious inflammation, which may show better efficacy when receiving the therapy particularly the celecoxib therapy. Besides, the patients with advanced OLGIM stage would preferably follow the doctor’s advice than other patients and complete the whole course of treatment. Many factors associated with efficacy were included in our study for analysis. The results of logistic regression analysis showed that eating habits are an independent factor for the IM reversal effect of LTEVB₁₂ therapy, which suggested that patients should change unhealthy eating habits while receiving treatment. At the end of the follow-up, four patients were diagnosed with HGIN and recommended to undergo digestive endoscopy surgery. Thus, the efficacy of complete therapy on such advanced lesions may be limited. A drawback of the study was that we did not obtain complete data for clinical symptoms, so we could not evaluate the effect. However, many studies have reported that celecoxib treatment did not increase adverse reactions or affect renal function[22]. This study was conducted in a single center, the sample size was limited, and the follow-up was only applied when 6 mo of therapy was finished, so the conclusion needs to be verified by a long-term follow-up prospective study.

Based on our findings, it is inappropriate to regard IM as the point of no return of gastric mucosal lesions. Correa et al[41] reported in 1990 that in the long-term follow-up, IM could reverse spontaneously in a few patients (0.044/person-year). Hwang et al[22] suggested that in the 10-year follow-up, eradication therapy of H. pylori could reverse 60% of IM lesions. Although some meta-analyses have shown that IM cannot be reversed after H. pylori eradication, there were still some clinical studies with long-term follow-up showed that IM could be reversed after H. pylori eradication. Correa et al[43] reported that eradication therapy could reverse not only the degree of AG, but also the IM in a randomized controlled trial. Leung et al[44] demonstrated that H. pylori eradication could inhibit the development of IM based on a randomized controlled trial with a 5-year follow-up. Kong et al[11] conducted a meta-analysis with the inclusion criteria using the Sydney system or the updated Sydney system. The result showed that H. pylori eradication was significantly related to improvement in IM in the antrum. Kodama et al[12] conducted a prospective 10-year follow-up of patients with IM after H. pylori eradication. Biopsy specimens were taken from five points of the stomach, as recommended by the updated Sydney system. IM scores of the lesser curvature of the corpus decreased gradually in the whole observation period and showed a significant decline after 6-year follow-up. These studies showed the importance of standardized methods of biopsy depending on OLGIM stage and long-term follow-up. Besides, Western and Chinese traditional medicines have a great effect on IM regression. In addition to LTEVB₁₂ and celecoxib mentioned in this study, our group recently also found that resveratrol could reduce IM through the PI3K/AKT/p-FoxO4 signaling pathway and had a potential reversing effect on those IM lesions especially caused by bile acid reflux[45]. Vitamins and other traditional Chinese medicines, such as Moluodan, have also been reported to have reversal effects on gastric precancerous lesions[46,47]. In general, IM should not be viewed as a point of no return of gastric mucosal lesions. The reversal effect of medicine is important for the prevention of GC and is beneficial for reducing the heavy burden of endoscopic follow-up of IM in China.

CONCLUSION

LTEVB₁₂ initial therapy and celecoxib rescue therapy can effectively decrease the OLG and OLGIM stages of IM patients to reduce the risk of GC. This therapy with integrative Chinese and western medicine may have good clinical application value in the prevention of GC. Moreover, this finding supports the insight that IM is not the point of no return among gastric precancerous lesions.
ARTICLE HIGHLIGHTS

Research background
A large number of intestinal metaplasia (IM) patients need to be effectively treated, which can successfully reduce the risk of gastric cancer (GC). Some medicines have showed the potential to reverse the IM lesion. It would help doctors in clinical practice and refute the concept that IM could not be reversed.

Research motivation
Lamb’s tripe extract and vitamin B12 capsule (LTEVB12) and celecoxib have been proved to reverse IM in past studies. But the IM regression effect of LTEVB12 and celecoxib still have to be evaluated thoroughly by operative link on gastritis assessment (OLGA) and operative link on the gastric intestinal metaplasia assessment (OLGIM) stages. What’s more, the combination of these two kinds of drugs may enhance the effect of IM regression.

Research objectives
This study aimed to validate the efficacy of LTEVB12 initial therapy and celecoxib rescue therapy on IM.

Research methods
This study was a retrospective cohort study. A total of 255 patients were included to receive LTEVB12 initial therapy in this study. The patients with failure of IM regression continued to celecoxib receive rescue therapy. After each therapy finished, patients underwent endoscopy and biopsy examination. OLGA and OLGIM stages were applied to evaluate the reversal of atrophic gastritis (AG) and IM.

Research results
For LTEVB12 initial therapy, the reversal rates of IM and AG were 52.95% and 48.24%, respectively. For celecoxib rescue therapy, the effective rates for IM and AG were 56.25% and 51.56%, respectively. The IM regression rate of complete therapy was up to 85.03% (P < 0.05). For both therapies, patients with high stages (III or IV) of both OLGA and OLGIM evaluation systems showed a higher IM or AG regression rate than those patients with low stages (I or II). Among high stage (OLGIM III and IV) patients, the IM regression rate was above 70% for each therapy.

Research conclusions
Each monotherapy could effectively reverse IM and AG. The LTEVB12 initial therapy and celecoxib rescue therapy, significantly increased the regression effect, which showed strong potential to reduce the risk of GC. IM may be not the point of no return among gastric precancerous lesions.

Research perspectives
LTEVB12 initial therapy and celecoxib rescue therapy can achieve better effect on IM regression compared with either monotherapy. IM could be reversed by clinical intervention.

REFERENCES


7 Wright NA. Gastric carcinogenesis: when is the point of no return? CA: Springer, 1998


Wu SR et al. LTEVB12 plus celecoxib reverses IM

10.1136/gutjnl-2011-300154


27 Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. *Gut* 2002; 51: 130-131 [PMID: 12077106 DOI: 10.1136/gut.51.1.130]


Retrospective Cohort Study

Clinical features and survival of patients with multiple primary malignancies

Xin-Kun Wang, Min-Hang Zhou

ORCID number: Xin-Kun Wang 0000-0002-9574-9019; Min-Hang Zhou 0000-0002-2094-4127.

Author contributions: Wang XK collected and analyzed the data, and drafted the work; Zhou MH performed the design of the work, the interpretation of data and revised the work; all authors read and approved the final manuscript.

Institutional review board statement: The study was approved by the institutional review board of our hospital (2020KY018-KS001).

Informed consent statement: The study was retrospective and the data were anonymous, so the requirement for informed consent was waived.

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

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

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

Xin-Kun Wang, Department of Radiology, the Fourth Medical Center, Chinese PLA General Hospital, Beijing 100048, China

Min-Hang Zhou, Department of Geriatric Oncology, the Fourth Medical Center, Chinese PLA General Hospital, Beijing 100048, China

Corresponding author: Min-Hang Zhou, MM, Attending Doctor, Department of Geriatric Oncology, the Fourth Medical Center, Chinese PLA General Hospital, No. 51 Fucheng Road, Beijing 100048, China. zhou_minhang@163.com

Abstract

BACKGROUND
Multiple primary malignancies (MPM) are characterized by two or more primary malignancies in the same patient, excluding relapse or metastasis of prior cancer. We aimed to elucidate the clinical features and survival of MPM patients.

AIM
To elucidate the clinical features and survival of MPM patients.

METHODS
A retrospective study of MPM patients was conducted in our hospital between June 2016 and June 2019. Overall survival (OS) was calculated using the Kaplan-Meier method. The log-rank test was used to compare the survival of different groups.

RESULTS
A total of 243 MPM patients were enrolled, including 222 patients with two malignancies and 21 patients with three malignancies. Of patients with two malignancies, 51 (23.0%) had synchronous MPM, and 171 (77.7%) had metachronous MPM. The most common first cancers were breast cancer (33, 14.9%) and colorectal cancer (31, 14.0%). The most common second cancers were non-small cell lung cancer (NSCLC) (66, 29.7%) and gastric cancer (24, 10.8%). There was no survival difference between synchronous and metachronous MPM patients (36.4 vs 35.3 mo, \( P = 0.809 \)). Patients aged > 65 years at diagnosis of the second cancer had a shorter survival than patients ≤ 65 years (28.4 vs 36.4 mo, \( P = 0.038 \)). Patients with distant metastasis had worse survival than patients without metastasis (20.4 vs 86.9 mo, \( P = 0.000 \)). Following multivariate analyses, age > 65 years and distant metastasis were independent adverse prognostic factors for OS.
CONCLUSION
During follow-up of a first cancer, the occurrence of a second or more cancers should receive greater attention, especially for common concomitant MPM, to ensure early detection and treatment of the subsequent cancer.

Key Words: Multiple primary malignancies; Overall survival; Prognostic factor; Distant metastasis; Age

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In the paper we investigated the clinical features and survival of 243 patients with multiple primary malignancies (MPM), including 222 patients with two malignancies and 21 patients with three malignancies. There was no survival difference between synchronous and metachronous MPM patients. After multivariate analyses, age > 65 years and distant metastasis were independent adverse prognostic factors for overall survival. In clinical procedure and follow-up of initial cancer, the occurrence of second or more cancer should be paid great attention to.

INTRODUCTION
Multiple primary malignancies (MPM) are characterized by two or more different primary malignancies in the same patient, excluding relapse or metastases of prior cancer[1]. An increased incidence of MPM has been observed with the rapid development of medical techniques and prolonged life expectancy[2,3]. The causes of MPM may be associated with genetic alterations, the environment and iatrogenic factors[4].

Colorectal cancer, breast cancer and head and neck cancer have been reported as the most common first primary malignancies, and lung cancer, breast cancer and colorectal cancer as the most common subsequent primary malignancies[5,6]. The most common MPM pairs were head and neck-lung cancer, and breast-gynecologic cancer[7]. According to the interval between initial cancer and subsequent cancer, MPM can be divided into synchronous MPM (within 6 mo) and metachronous MPM (more than 6 mo)[8]. Metachronous MPM account for most of the patients with MPM, with a 5-year OS, ranging from 61% to 68%[7,9]. In some reports, patients with metachronous MPM had better survival than patients with synchronous MPM[7,9], while this survival advantage was not observed in the study by Xu and Gu[10].

In the present study, we retrospectively analyzed the clinical features and survival of patients with MPM in our hospital over the past 3 years, in order to provide helpful information for the diagnosis, treatment, prognosis and follow-up of these patients.

MATERIALS AND METHODS

Patients
A retrospective study of MPM patients was conducted in our hospital between June 2016 and June 2019. The diagnosis of each malignancy in MPM patients was identified by histopathology. Hematological malignancies were excluded in our study, and only solid malignant tumors were included. A total of 27055 patients with solid malignant tumors were consecutively identified. Of these patients, 260 had MPM. After further review, 17 patients were excluded from our study, including 11 patients with no pathological diagnosis of one tumor, and 6 patients who were lost to follow-up. Therefore, a total of 243 MPM patients with complete clinical and follow-up data were enrolled in the study, including 222 patients with two malignancies and 21 patients with three malignancies.
with three malignancies. In patients with two primary malignancies, synchronous MPM was defined as two malignancies diagnosed within 6 mo, and metachronous MPM as two malignancies diagnosed within more than 6 mo between the first and second cancer. The study was approved by the institutional review board of our hospital (2020KY018-KS001).

**Statistical analysis**
Continuous and categorical variables were summarized as the median with range, and the count with percentage, respectively. For patients with two malignancies, overall survival (OS) was defined as the time from diagnosis of the second malignancy to death due to any cause, or to the last follow-up. For patients with three malignancies, OS was defined as the time from diagnosis of the third malignancy to death due to any cause, or to the last follow up. The end of follow-up was December 2019. OS was calculated using the Kaplan-Meier method. The log-rank test was used to compare the survival of different groups. Multivariate Cox regression models were used to find the prognostic factors for OS. All the data were analyzed using IBM SPSS statistics software (version 22). \( P \) value < 0.05 was considered statistically significant.

**RESULTS**
A total of 26795 patients with one solid malignant tumor were found. The five most common cancers were non-small cell lung cancer (NSCLC) (18.3%), colorectal cancer (12.5%), breast cancer (10.6%), gastric cancer (9.4%) and liver cancer (7.3%). Patients with MPM accounted for 0.96% (260/27055) of all patients with solid malignant tumor.

**Characteristics of patients with two malignancies**
A total of 243 patients with MPM were included in our study. Of these patients, 222 with two malignancies were identified, and the demographics and clinical characteristics of these patients are shown in Table 1. Fifty-one patients (23.0%) had synchronous MPM, and 171 patients (77.7%) had metachronous MPM. In the synchronous, metachronous and total MPM groups, 32 patients (62.7%), 87 patients (50.9%) and 119 patients (53.6%) were male, respectively; the median age at diagnosis of the first cancer was 62 years, 55 years and 56 years respectively; the median interval between the first and second cancer diagnoses was 0.2 mo, 73.2 mo and 43.6 mo, respectively; distant metastasis was found in 16 (31.4%) patients, 83 (48.5%) patients and 99 (44.6%) patients, respectively.

In 222 patients with two malignancies, the most common first cancers were breast cancer (33, 14.9%), colorectal cancer (31, 14.0%), and gastric cancer (17, 7.7%). The most common second cancers were NSCLC (66, 29.7%), gastric cancer (24, 10.8%) and esophageal cancer, liver cancer (16, 7.2%), respectively. In 51 synchronous MPM patients, the most common first cancer was esophageal cancer (9, 17.6%), colorectal cancer (8, 15.7%) and bladder cancer, thyroid cancer, hypopharyngeal cancer (4, 7.8%, respectively). The most common second cancers were NSCLC (12, 23.5%), gastric cancer (9, 17.6%) and esophageal cancer, renal cancer (6, 11.8%, respectively). In 171 metachronous MPM patients, the most common first cancers were breast cancer (31, 18.1%), colorectal cancer (23, 13.7%) and gastric cancer (14, 8.2%). The most common second cancers were NSCLC (54, 31.6%), gastric cancer (15, 8.8%) and liver cancer (13, 7.6%).

**Most common MPM in patients with two malignancies and their survival**
In the 222 patients with two malignancies, the most common MPM and their median OS are shown in Table 2. Twelve patients were found to have NSCLC and breast cancer, and the median OS of these patients was 79.8 mo (Figure 1A). Ten patients were found to have NSCLC and gastric cancer, and the median OS was 16.7 mo (Figure 1B). Colorectal cancer and gastric cancer were identified in ten patients, with the median OS not reached (Figure 1C). Esophageal cancer and gastric cancer were identified in nine patients, with a median OS of 36.2 mo (Figure 1D).

**Prognostic factors of OS in patients with two malignancies**
The univariate and multivariate analyses of prognostic factors for OS inpatients with two malignancies are presented in Table 3. The median OS in all 222 patients was 35.4 mo (Figure 2A). The median OS in synchronous MPM and metachronous MPM patients were 36.4 mo and 35.3 mo, respectively, which was not significantly different (Figure 2B). The median OS between male and female patients was also not
Table 1 The characteristics of patients with two malignancies, \( n \% \)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Synchronous MPM</th>
<th>Metachronous MPM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>51 (23.0)</td>
<td>171 (77.0)</td>
<td>222 (100)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32 (62.7)</td>
<td>87 (50.9)</td>
<td>119 (53.6)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (37.3)</td>
<td>84 (49.1)</td>
<td>103 (46.4)</td>
</tr>
<tr>
<td>Age in yr, median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First cancer</td>
<td>62 (32-84)</td>
<td>55 (19-87)</td>
<td>56 (19-87)</td>
</tr>
<tr>
<td>Second cancer</td>
<td>62 (32-84)</td>
<td>64 (28-90)</td>
<td>64 (28-90)</td>
</tr>
<tr>
<td>The most common sites in first cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(^{st})</td>
<td>Esophagus, 9 (17.6)</td>
<td>Breast, 31 (18.1)</td>
<td>Breast, 33 (14.9)</td>
</tr>
<tr>
<td>2(^{nd})</td>
<td>Colorectum, 8 (15.7)</td>
<td>Colorectum, 23 (13.7)</td>
<td>Colorectum, 31 (14.0)</td>
</tr>
<tr>
<td>3(^{rd})</td>
<td>Bladder/thyroid/hypopharynx, 4 (7.8), respectively</td>
<td>Stomach, 14 (8.2)</td>
<td>Stomach, 17 (7.7)</td>
</tr>
<tr>
<td>The most common sites in second cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(^{st})</td>
<td>NSCLC, 12 (23.5)</td>
<td>NSCLC, 54 (31.6)</td>
<td>NSCLC, 66 (29.7)</td>
</tr>
<tr>
<td>2(^{nd})</td>
<td>Stomach, 9 (17.6)</td>
<td>Stomach, 15 (8.8)</td>
<td>Stomach, 24 (10.8)</td>
</tr>
<tr>
<td>3(^{rd})</td>
<td>Esophagus/kidney, 6 (11.8), respectively</td>
<td>Liver, 13 (7.6)</td>
<td>Esophagus/liver, 16 (7.2), respectively</td>
</tr>
<tr>
<td>Median interval (range) between the first and second cancers (mo)</td>
<td>0.2 (0-5.9)</td>
<td>73.2 (6.3-536.8)</td>
<td>43.6 (0-536.8)</td>
</tr>
<tr>
<td>Metastasis</td>
<td>16 (31.4)</td>
<td>83 (48.5)</td>
<td>99 (44.6)</td>
</tr>
<tr>
<td>Median overall survival in mo</td>
<td>36.4</td>
<td>35.3</td>
<td>35.4</td>
</tr>
</tbody>
</table>

MPM: Multiple primary malignancies; NSCLC: Non-small cell lung cancer.

Table 2 The most common multiple primary malignancies in patients with two malignancies

<table>
<thead>
<tr>
<th>Malignancies</th>
<th>Total</th>
<th>Synchronous MPM</th>
<th>Metachronous MPM</th>
<th>Median OS in mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC and breast cancer</td>
<td>12</td>
<td>2</td>
<td>10</td>
<td>79.8</td>
</tr>
<tr>
<td>NSCLC and gastric cancer</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>16.7</td>
</tr>
<tr>
<td>Colorectal cancer and gastric cancer</td>
<td>10</td>
<td>3</td>
<td>7</td>
<td>Not reached</td>
</tr>
<tr>
<td>Esophageal cancer and gastric cancer</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td>36.2</td>
</tr>
<tr>
<td>NSCLC and bladder cancer</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>31.2</td>
</tr>
<tr>
<td>NSCLC and cervical cancer</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>35.5</td>
</tr>
<tr>
<td>NSCLC and thyroid cancer</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>Not reached</td>
</tr>
<tr>
<td>NSCLC and colorectal cancer</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>Not reached</td>
</tr>
<tr>
<td>NSCLC and esophageal cancer</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

MPM: Multiple primary malignancies; NSCLC: Non-small cell lung cancer; OS: Overall survival.

significantly different. However, patients aged \( > 65 \) years at the second cancer diagnosis had a shorter survival than patients \( \leq 65 \) years \((28.4 \text{ mo} \text{ vs} 36.4 \text{ mo}, P = 0.038; Figure 2C). Patients with distant metastasis had worse survival than patients without metastasis \((20.4 \text{ mo} \text{ vs} 86.9 \text{ mo}, P = 0.000; Figure 2D). Furthermore, multivariate analyses showed that age and metastases remained statistically different, indicating that age \( > 65 \) years and distant metastasis were independent adverse prognostic factors.
Table 3 Univariate analysis and multivariate analysis of the prognostic factors of overall survival in patients with two malignancies

<table>
<thead>
<tr>
<th>Factors</th>
<th>Cases</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median OS in mo</td>
<td>P</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.114</td>
</tr>
<tr>
<td>Male</td>
<td>119</td>
<td>31.2</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>105</td>
<td>37.1</td>
<td></td>
</tr>
<tr>
<td>Age at second cancer (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 65</td>
<td>128</td>
<td>36.4</td>
<td>0.038</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>94</td>
<td>28.4</td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>No</td>
<td>123</td>
<td>86.9</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>99</td>
<td>20.4</td>
<td></td>
</tr>
<tr>
<td>MPM</td>
<td></td>
<td></td>
<td>0.809</td>
</tr>
<tr>
<td>Synchronous</td>
<td>51</td>
<td>36.4</td>
<td></td>
</tr>
<tr>
<td>Metachronous</td>
<td>171</td>
<td>35.3</td>
<td></td>
</tr>
</tbody>
</table>

MPM: Multiple primary malignancies; OS: Overall survival.

Figure 1 Overall survival of patients with different cancers. A: Twelve patients with non-small cell lung cancer and breast cancer; B: Ten patients with non-small cell lung cancer and gastric cancer; C: Ten patients with colorectal cancer and gastric cancer; D: Nine patients with esophageal cancer and gastric cancer.
Figure 2 Overall survival of patients with two malignancies. A: Two hundred and twenty-two patients with two primary malignancies; B: Metachronous multiple primary malignancies (MPM) patients vs synchronous MPM patients; C: Patients ≤ 65 years vs patients > 65 years; D: Patients with metastasis vs patients without metastasis. MPM: Multiple primary malignancies.

Characteristics and survival of patients with three malignancies

A total of 21 patients with three malignancies were identified in our study. Their clinical features are shown in Table 4 and Table 5. Eleven patients (52.4%) were male, and 12 patients (57.1%) had distant metastases. The median age at the first, second and third cancer was 47 years, 54 years and 57 years, respectively. The most common cancers in all patients were colon cancer (9, 14.3%), rectal cancer (7, 11.1%) and breast cancer (5, 7.9%). The median OS from diagnosis of the third cancer was 14.4 mo (Figure 3).

DISCUSSION

In this study, we retrospectively analyzed the clinical features and survival of 243 MPM patients, including 222 patients with two malignancies and 21 patients with three malignancies. The most common MPM were NSCLC and breast cancer (12 cases), NSCLC and gastric cancer (10 cases), and colorectal cancer and gastric cancer (10 cases), with the median OS of 79.8 mo, 16.7 mo and not reached, respectively. The median OS of patients with two malignancies and three malignancies were 35.4 mo and 14.4 mo, respectively. Age > 65 years and distant metastases were independent adverse prognostic factors for OS in patients with two malignancies.

In a retrospective study of 278 MPM patients, 120 (43%) patients presented with synchronous MPM, and 158 patients (57%) with metachronous MPM [9]. In our study, we had fewer patients with synchronous MPM (51, 23%) and more patients with three
Table 4 The clinical features of 21 patients with three malignancies

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>First cancer</th>
<th>Second cancer</th>
<th>Third cancer</th>
<th>Metastases</th>
<th>Outcome</th>
<th>OS since third cancer in mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Parotid cancer</td>
<td>Colon cancer</td>
<td>Penile cancer</td>
<td>Yes</td>
<td>Dead</td>
<td>0.6</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Small cell lung cancer</td>
<td>Colon cancer</td>
<td>Soft tissue sarcoma</td>
<td>No</td>
<td>Dead</td>
<td>14.4</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Gastric cancer</td>
<td>Liver cancer</td>
<td>Rectal cancer</td>
<td>Yes</td>
<td>Dead</td>
<td>14.0</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Rectal cancer</td>
<td>Renal cancer</td>
<td>Colon cancer</td>
<td>No</td>
<td>Alive</td>
<td>23.1</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Colon cancer</td>
<td>Bladder cancer</td>
<td>Renal pelvis cancer</td>
<td>No</td>
<td>Alive</td>
<td>67.5</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>Soft tissue sarcoma</td>
<td>Colon cancer</td>
<td>Bladder cancer</td>
<td>Yes</td>
<td>Dead</td>
<td>4.8</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>Colon cancer</td>
<td>Endometrial cancer</td>
<td>Breast cancer</td>
<td>Yes</td>
<td>Alive</td>
<td>23.8</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>Breast cancer</td>
<td>Parotid cancer</td>
<td>Neuroendocrine carcinoma</td>
<td>Yes</td>
<td>Dead</td>
<td>9.5</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>Bladder cancer</td>
<td>Thyroid cancer</td>
<td>Ureteral cancer</td>
<td>No</td>
<td>Alive</td>
<td>18.9</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>Rectal cancer</td>
<td>Colon cancer</td>
<td>Cholangiocarcinoma</td>
<td>Yes</td>
<td>Dead</td>
<td>6.0</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>Laryngeal cancer</td>
<td>Esophageal cancer</td>
<td>Non-small cell lung cancer</td>
<td>No</td>
<td>Alive</td>
<td>21.5</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>Thyroid cancer</td>
<td>Laryngeal cancer</td>
<td>Rectal cancer</td>
<td>Yes</td>
<td>Dead</td>
<td>10.2</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>Bladder tumor</td>
<td>Colon cancer</td>
<td>Non-small cell lung cancer</td>
<td>No</td>
<td>Dead</td>
<td>12.7</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>Laryngeal cancer</td>
<td>Renal pelvis cancer</td>
<td>Bladder cancer</td>
<td>No</td>
<td>Dead</td>
<td>12.9</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>Rectal cancer</td>
<td>Thyroid cancer</td>
<td>Breast cancer</td>
<td>Yes</td>
<td>Dead</td>
<td>95.4</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>Skin squamous cell cancer</td>
<td>Skin basal cell carcinoma</td>
<td>Endometrial cancer</td>
<td>Yes</td>
<td>Alive</td>
<td>57.7</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>Gallbladder cancer</td>
<td>Endometrial cancer</td>
<td>Rectal cancer</td>
<td>No</td>
<td>Alive</td>
<td>15.4</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>Endometrial cancer</td>
<td>Rectal cancer</td>
<td>Pancreatic cancer</td>
<td>Yes</td>
<td>Dead</td>
<td>6.0</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>Breast cancer</td>
<td>Thymic cancer</td>
<td>Choriocarcinoma</td>
<td>No</td>
<td>Alive</td>
<td>18.8</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>Breast cancer</td>
<td>Thyroid cancer</td>
<td>Liver cancer</td>
<td>Yes</td>
<td>Alive</td>
<td>9.0</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>Prostate cancer</td>
<td>Gastric cancer</td>
<td>Colon cancer</td>
<td>Yes</td>
<td>Dead</td>
<td>7.9</td>
</tr>
</tbody>
</table>

F: Female; M: Male; OS: Overall survival.

malignancies. The median interval between two cancers in patients with metachronous MPM in the above study was 30.98 mo, less than the median interval in our study of 73.2 mo. In the above study, the most common first cancers were breast, head and neck, and colorectal cancer; the most common second cancers were breast, colorectal and uterine body cancer. In our study, breast and colorectal cancer were also the most common. In addition, other common cancers in our study were NSCLC and digestive system malignancies, such as stomach, esophagus and liver, which were different from those in the above report.

The survival differences of synchronous and metachronous MPM have been reported inconsistently in different studies. Some reported that survival in patients with metachronous MPM was better than in synchronous MPM\(^7,9\). However, no survival differences between synchronous and metachronous MPM were noted in our study, and in another study\(^10\). Of note, the starting point of calculated survival time in metachronous MPM was not consistent in previous studies, some were calculated from the date of the first cancer diagnosis and some from the date of the last cancer diagnosis. Besides, different cancer constituents may account for the inconsistent results.

In a report of 350 MPM patients with lung cancer, the most common associated malignancies were esophageal cancer, breast cancer, gastric cancer and colorectal cancer\(^11\). In another report of 268 metachronous MPM patients with lung cancer, colorectal cancer, breast cancer and gastric cancer were the most common associated primary cancers\(^12\). Unfortunately, the survival of patients with lung MPM was not reported. Similarly, in our study, the most common concomitant malignancies in MPM patients with NSCLC were breast cancer, gastric cancer and bladder cancer, with a
Table 5 The characteristics of patients with three malignancies, n (%)  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>21</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (47.6)</td>
</tr>
<tr>
<td>Age in yr, median (range)</td>
<td></td>
</tr>
<tr>
<td>First cancer</td>
<td>47 (18-74)</td>
</tr>
<tr>
<td>Second cancer</td>
<td>54 (33-87)</td>
</tr>
<tr>
<td>Third cancer</td>
<td>57 (34-89)</td>
</tr>
<tr>
<td>The most common cancers</td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>9 (14.3)</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>5 (7.9)</td>
</tr>
<tr>
<td>Bladder/endometrial/thyroid cancer</td>
<td>4 (6.3), respectively</td>
</tr>
<tr>
<td>Laryngeal cancer</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>Metastasis</td>
<td>12 (57.1)</td>
</tr>
<tr>
<td>Median OS since third cancer in mo</td>
<td>14.4</td>
</tr>
</tbody>
</table>

OS: Overall survival.

Figure 3 Overall survival of 21 patients with three malignancies.

In a report of 55 MPM patients with colorectal cancer, stomach cancer was the most commonly associated lesion [13]. In another study of 117 MPM patients with colorectal cancer, the most commonly associated cancer was gastric cancer, followed by lung and breast cancer [14]. In our study, gastric cancer was also the most frequently observed associated cancer in patients with colorectal cancer. A total of ten patients with colorectal and gastric cancer were found in our 222 MPM patients with two malignancies. The median OS of patients with colorectal and gastric cancer was not reached.
In a respective study of 170 MPM patients\cite{10}, 17 cases with esophageal and gastric cancer were found. The median survival of 42 gastrointestinal MPM, including the above 17 cases, was 40 mo, which was close to our 36.2 mo in nine patients with esophageal and gastric cancer. Chen et al\cite{15} analyzed 192 patients with esophageal and gastric cancer from a database in the United States, and found that the median OS of these patients was approximately 59 mo, but with longer follow-up time, none of these patients survived.

Following univariate and multivariate analyses, older age and distant metastasis were independent poor prognostic factors for OS. In the study by Etiz et al\cite{7}, elderly and young patients showed no differences in survival. However, Wang et al\cite{11} reported that the OS of patients < 60 years was significantly better than that of patients ≥ 60 years, which was also showed in the multivariate analysis. It is generally believed that cancer patients with distant metastasis have a poor prognosis\cite{16,17}. Distant metastasis was also an adverse prognostic factor in our MPM patients.

In our 243 MPM patients, 21 patients with three primary malignancies were identified, whereas only two patients with three primary malignancies in 170 MPM patients were found in the study by Xu and Gu\cite{10}. Compared with our study, the study by Xu and Gu\cite{10} was conducted at least 6 years ago, and insufficient diagnosis and therapy may have resulted in the fewer patients being diagnosed with three malignancies. In another report of 30 patients with three primary malignancies\cite{18}, the median OS from the initial cancer diagnoses was 11.2 years. Our 21 patients with three malignancies had a median OS of 14.4 mo from the third cancer diagnoses. Due to the 10-years interval between the first and third cancer in our study, it is justified to consider that these two patient groups had a similar survival.

There are two limitations in our respective study. Firstly, the prognostic characteristics and treatment response of different cancers vary widely. Therefore, cancer types and treatment methods are important prognostic factors. However, these two factors were not included in our survival analysis. Secondly, MPM patients, especially those with three primary malignancies, may have potential genetic and environmental pathogenic factors, which are important in cancer prevention and treatment. However, these underlying pathogenic factors were not investigated in our study and deserve further detailed study.

**CONCLUSION**

During the diagnosis, treatment and follow-up of the initial cancer, more attention should be paid to the occurrence of a second, or even a third cancer in patients with MPM, to ensure early detection and treatment of the subsequent cancer. In particular, for common MPM pairs, such as NSCLC and breast/gastric cancer, colorectal and gastric cancer, the risk of concomitant MPM should be closely monitored.

**ARTICLE HIGHLIGHTS**

**Research background**

Multiple primary malignancies (MPM) are characterized by two or more primary malignancies in the same patient, excluding relapse or metastasis of prior cancer.

**Research motivation**

The clinical features and survival of MPM patients are not clear.

**Research objectives**

We aimed to elucidate the clinical features and survival of MPM patients.

**Research methods**

A retrospective study of MPM patients was conducted in our hospital between June 2016 and June 2019. Overall survival (OS) was calculated using the Kaplan-Meier method.

**Research results**

A total of 243 patients with MPM, including 222 patients with two malignancies and 21 patients with three malignancies. Following multivariate analyses, age > 65 years
and distant metastasis were independent adverse prognostic factors for OS.

Research conclusions
During the diagnosis, treatment and follow-up of the initial cancer, more attention should be paid to the occurrence of a second, or even a third cancer in patients with MPM.

Research perspectives
For common MPM pairs, such as NSCLC and breast/gastric cancer, colorectal and gastric cancer, the risk of concomitant MPM should be closely monitored, to ensure early detection and treatment of the subsequent cancer.

REFERENCES

Thoracoscopic segmentectomy and lobectomy assisted by three-dimensional computed-tomography bronchography and angiography for the treatment of primary lung cancer

Yun-Jiang Wu, Qing-Tong Shi, Yong Zhang, Ya-Li Wang

BACKGROUND
Anatomical segmentectomy has been proposed as a substitution for lobectomy for early-stage lung cancer. However, it requires technical meticulousness due to the complex anatomical variations of segmental vessels and bronchi.

AIM
To assess the safety and feasibility of three-dimensional computed-tomography bronchography and angiography (3D-CTBA) in performing video-assisted thoracoscopic surgery (VATS) for lung cancers.

METHODS
In this study, we enrolled 123 patients who consented to undergo thoracoscopic segmentectomy and lobectomy assisted by 3D-CTBA between May 2017 and June 2019. The image data of enhanced computed tomography (CT) scans was reconstructed three-dimensionally by the Mimics software. The results of preoperative 3D-CTBA, in combination with intraoperative navigation, guided the surgery.

RESULTS
A total of 59 women and 64 men were enrolled, of whom 57 (46.3%) underwent segmentectomy and 66 (53.7%) underwent lobectomy. The majority of tumor appearance on CT was part-solid ground-glass nodule (pGGN; 55.3%). The mean duration of chest tube placement was 3.5 ± 1.6 d, and the average length of
INTRODUCTION

The increased popularity of health checkups and recent advances in high-resolution computed-tomography (CT) imaging have improved the early detection of lung cancer[1], ushering in a new era of less-invasive surgery for this disease. Currently, video-assisted thoracoscopic surgery (VATS) is being assessed as an alternative to thoracotomy for primary lung cancers[2]. However, a lack of stereoscopic vision and the existence of anatomical variations create problems for surgeons during VATS, which can lead to unexpected complications, such as atelectasis, bleeding, pulmonary infection, and inadequate surgical margin[3]. Therefore, the surgeon must have an accurate understanding of the patient’s pulmonary anatomy before surgery, especially an inexperienced surgeon.

Anatomical segmentectomy has been proposed as a substitution for lobectomy for early-stage lung cancer, which could produce oncological results equivalent to those of lobectomy[4]. However, there is an ongoing dispute over the safety and outcomes of VATS segmentectomy compared with those of lobectomy[5]. The segmentectomy can retain a maximal proportion of healthy lung tissue, which is beneficial to protecting postoperative lung function and improving quality of life. However, it requires technical meticulousness due to the complex anatomical variations of segmental vessels and bronchi. In addition, it remains highly controversial due to concerns about increased locoregional recurrence of lung cancer, higher rates of complications, and inadequate surgical margin[6]. Therefore, constructing a three-dimensional (3D) image that can provide stereoscopic vision and accurately map out targeted structures is desirable when planning for VATS segmentectomy[7].
Currently, the new 3D imaging software packages widely used across the world are not specifically designed for thoracic surgery. Vessel reconstruction by 3D computed tomography and angiography (3D-CTA) is now performed well, but reconstructions of the bronchus are influenced by multiple factors, and the distance from the lesion to the predetermined cutting margin is hard to measure accurately\[8\]. Our center is exploring reconstruction of preoperative 3D computed-tomography bronchography and angiography (3D-CTBA) using Mimics software (Materialise, Leuven, Belgium), which offers powerful 3D construction capability and allows for better 3D visualization of pulmonary anatomy. Therefore, we designed this study to evaluate the efficacy of 3D-CTBA using Mimics in performing accurate VATS segmentectomy and lobectomy, employing a series of typical examples.

**MATERIALS AND METHODS**

**Patient inclusion criteria and preoperative evaluation**

The study protocol was approved and supervised by the Ethics Committee of the Affiliated Hospital of Yangzhou University, Yangzhou, China. All patients signed an informed-consent form. Between May 2017 and June 2019, we performed VATS segmentectomy and lobectomy via 3D-CTBA on 123 patients. Our inclusion criteria for VATS lobectomy in lung cancer were good lung reserve, clinical T1–T3N0 stage. Patients with multi-lobe resection, lymph node metastasis, or small-cell lung cancer were excluded. Based on United States National Comprehensive Cancer Network (NCCN) guidelines for lung cancer\[9\], indications for VATS segmentectomy were as follows: (1) Poor lung reserve or other major comorbidity that contraindicated lobectomy; and (2) Peripheral nodule ≤ 2 cm with at least 1 of the following: (a) Pure adenocarcinoma in situ (AIS) histology; (b) Nodule had ≥ 50% ground-glass appearance (GGO) on CT; and (c) Radiological surveillance confirmed a long doubling time (≥ 400 d). Exclusion criteria included carcinoid tumor, small-cell lung cancer, lymph node metastasis, wedge resections, and multiple primary lung cancer. Data from patient medical records consisted of demographics, surgical technique, duration of surgery, blood loss, perioperative complications, length of postoperative hospital stay, tumor size, and histopathological subtype. The preoperative assessment included enhanced CT of chest and abdomen, flexible bronchoscopy, arterial blood gas analysis, spirometry, echocardiography (ECG), enhanced brain magnetic resonance imaging (EMRI), and positron emission tomography (PET). PET/CT for all patients showed N0 stage, and the final pathological N0-stage was confirmed by pathological examination. We obtained patients’ preoperative characteristics and surgical outcomes from the inpatient database for analysis. Mortality within 30 d was also recorded.

**Preoperative 3D-CTBA imaging reconstruction**

We performed preoperative enhanced-CT scans on all patients using a multidetector CT (MDCT) unit (Somatom Definition Flash; Siemens Healthcare, Erlangen, Germany). Scanning range was from the thoracic-inlet plane to the posterior costodiaphragmatic-angle plane. The thickness of the construction layer was 1.0 mm. Afterward, we transmitted the image data to the computer, saved it in Digital Imaging and Communications in Medicine (DICOM) format, and reconstructed it using Mimics software version 21. The pulmonary anatomy was reconstructed 3-dimensionally on the basis of the difference in CT values and the surgeon’s understanding. We distinguished the pulmonary bronchus, artery, and vein from one another and marked them out in distinct colors (Figure 1). Preoperative 3D-CTBA was performed to analyze anatomical variations, detect the exact location of the tumor, and ensure its relationship to the surrounding structure. The 3D-CTBA images were assessed and interpreted by at least 2 attending surgeons and 1 radiologist, who reached a consensus.

**Preoperative surgical simulation**

Multidimensional 3D-CTBA views synergistically display the size, shape, and location of the tumor and its relationship to the surrounding structure. Because the lung should be resected with sufficient surgical margin, corresponding arteries, veins, and bronchi should be identified on the 3D images. During the simulation, surgeons can accurately identify and label targeted structures on the 3D-CTBA video and design meticulous plans to perform minimal unit resection with sufficient surgical margin and optimal intersegmental borders to protect postoperative lung function. Meanwhile, the reconstructed 3D-CTBA image can be rotated and displayed horizontally or vertically in the operating room for accurate intraoperative navigation.
Figure 1 Preoperative flow diagram of three-dimensional reconstruction technique using Mimics software. The pulmonary bronchus, artery and vein were distinguished from one another and marked out with different colors: white, bronchus; red, pulmonary artery; purple, pulmonary vein. 3D: 3-dimensional; CT: Computed-tomography.

**Surgical procedure oriented by 3D-CTBA**

We precisely located pulmonary nodules using CT-guided hookwire combined with 3D images. Afterwards, we performed VATS assisted by 3D-CTBA with patients under general anesthesia in the lateral-decubitus position with 1-lung ventilation. We made a 1.5-cm incision for thoracoscopic observation in the 7th or 8th intercostal space (ICS) at the midaxillary line, through which we inserted a 30° thoracoscope. A second incision, about 4 cm long, was made through the 4th or 5th ICS between the anterior axillary and midclavicular lines as the main operating hole. Next, a 2-cm incision was made through the 7th or 8th ICS between the posterior scapular and posterior axillary lines as the auxiliary operating hole. The 3D-CTBA image enabled the surgeon to secure a sufficient surgical margin within which the involved structure could be meticulously resected. Oriented by 3D-CTBA, we maintained the intersegmental veins and defined intersectional boundaries using an improved inflation-deflation method [8]. Anatomical resection of the pulmonary parenchyma was performed along inflation-deflation lines with 2-3 endoscopic staplers. During the procedure of VATS Lobectomy, systematic lymph node dissection was mandatory. The #10, #11, and #5-7 nodes of the left lung were all dissected, while the #10, #11, #2, #4, and #7 nodes of the right lung accepted routine dissection. In segmentectomy, the #10-12 lymph nodes should be dissected. Mediastinal lymph node sampling was performed for #5-7 nodes on the left, and #2, #4, and #7 nodes on the right. We incised the targeted structure using optimal surgical manipulation in order to reduce lung compression and air leakage and to preserve maximal postoperative lung function. At the end of surgery, we inserted a 28 French (28F) chest tube.

**RESULTS**

**Patients’ characteristics and oncological features**

The demographic and preoperative characteristics of patients enrolled in this study are listed in Table 1. Patients included a total of 59 women and 64 men, of whom 57 (46.3%) underwent VATS segmentectomy and 66 (53.7%) underwent lobectomy. One patient whose tumor size was 25 mm consented to a compromised segmentectomy due to poor pulmonary reserve. The median age was 61.4 ± 9.8 years (range: 39.0–80.0
Table 1 Characteristics and postoperative complications of patients receiving video-assisted thoracoscopic surgery assisted by three-dimensional computed-tomography bronchography and angiography

<table>
<thead>
<tr>
<th>Variable</th>
<th>Segmentectomy (n = 57)</th>
<th>Lobectomy (n = 66)</th>
<th>Total (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), yr</td>
<td>59.3 ± 10.8 (39.0-75.0)</td>
<td>63.2 ± 8.5 (44.0-80.0)</td>
<td>61.4 ± 9.8 (39.0-80.0)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31 (54.4%)</td>
<td>28 (42.4%)</td>
<td>59 (48.0%)</td>
</tr>
<tr>
<td>Male</td>
<td>26 (45.6%)</td>
<td>38 (57.6%)</td>
<td>64 (52.0%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (24.6%)</td>
<td>11 (16.7%)</td>
<td>25 (20.3%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (10.5%)</td>
<td>4 (6.1%)</td>
<td>10 (8.1%)</td>
</tr>
<tr>
<td>COPD</td>
<td>5 (8.8%)</td>
<td>7 (10.6%)</td>
<td>12 (9.8%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (1.8%)</td>
<td>2 (3.0%)</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>Operative time, mean (range), min</td>
<td>129.8 ± 16.1 (105-180)</td>
<td>125.2 ± 11.7 (105-160)</td>
<td>113.4 ± 19.7 (20-150)</td>
</tr>
<tr>
<td>Blood loss, mean (range), mL</td>
<td>48.8 ± 26.2 (20-150)</td>
<td>79.5 ± 34.0 (20-220)</td>
<td>65.3 ± 34.2 (20-220)</td>
</tr>
<tr>
<td>Duration of chest tube placement, mean (range), d</td>
<td>3.1 ± 1.1 (2.0-9.0)</td>
<td>3.8 ± 1.9 (2.0-10.0)</td>
<td>3.5 ± 1.6 (2.0-10.0)</td>
</tr>
<tr>
<td>Postoperative hospital stay, mean (range), d</td>
<td>6.4 ± 1.3 (5.0-12.0)</td>
<td>7.1 ± 2.2 (5.0-15.0)</td>
<td>6.8 ± 1.8 (5.0-15.0)</td>
</tr>
<tr>
<td>Tumor diameter, mean (range), mm</td>
<td>10.5 ± 4.9 (5.0-25.0)</td>
<td>23.4 ± 12.1 (8.0-60.0)</td>
<td>17.4 ± 11.4 (5.0-60.0)</td>
</tr>
<tr>
<td>Appearance on CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure GGO</td>
<td>12 (21.1%)</td>
<td>1 (1.5%)</td>
<td>13 (10.6)</td>
</tr>
<tr>
<td>p GGO</td>
<td>45 (78.9%)</td>
<td>23 (34.8%)</td>
<td>68 (55.3%)</td>
</tr>
<tr>
<td>Solid</td>
<td>0 (0%)</td>
<td>42 (63.6%)</td>
<td>42 (34.1%)</td>
</tr>
<tr>
<td>Histological types</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>56 (98.2%)</td>
<td>56 (84.8%)</td>
<td>112 (91.1%)</td>
</tr>
<tr>
<td>AIS</td>
<td>8 (14.0%)</td>
<td>3 (4.5%)</td>
<td>11 (8.9%)</td>
</tr>
<tr>
<td>MIA</td>
<td>20 (35.1%)</td>
<td>1 (1.5%)</td>
<td>21 (17.1%)</td>
</tr>
<tr>
<td>IA</td>
<td>28 (49.1%)</td>
<td>52 (78.8%)</td>
<td>80 (65.0%)</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>1 (1.8%)</td>
<td>7 (10.6%)</td>
<td>8 (6.5%)</td>
</tr>
<tr>
<td>Others</td>
<td>0 (0%)</td>
<td>3 (4.5%)</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>2 (3.5%)</td>
<td>8 (12.1%)</td>
<td>10 (8.1%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 (0%)</td>
<td>1 (1.5%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Prolonged air leakage (&gt; 5 d)</td>
<td>2 (3.5%)</td>
<td>1 (1.5%)</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>0 (0%)</td>
<td>6 (9.1%)</td>
<td>6 (4.9%)</td>
</tr>
<tr>
<td>Absent</td>
<td>55 (96.5%)</td>
<td>58 (87.9%)</td>
<td>113 (91.9%)</td>
</tr>
<tr>
<td>Conversion rate</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>30-d mortality</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Postoperative ICU stay</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

AIS: Adenocarcinoma in situ; CT: Computed tomography; GGO: Ground-glass appearance; IA: Invasive adenocarcinoma; ICU: Intensive-care unit; MIA: Minimally invasive adenocarcinoma.

years). Tumor appearance on CT was mostly part-solid ground-glass nodule (pGNN; 55.3%); solid nodules were second most common (34.1%), followed by pure ground glass nodule (GGN; 10.6%). Mean duration of chest tube placement was 3.5 ± 1.6 d and the average postoperative hospital stay was 6.8 ± 1.8 d without intensive-care unit
The right lower (lobe (underwent segmentectomy and lobectomy. Anatomical resection of the right upper hemorrhages, postoperative ICU stays, or 30-d mortalities.

Notably, there was no intraoperative massive with prolonged air leak lasting > 5 d, which prolonged their hospital stays. No other 5–60 mm). Surgical complications included one patient with pneumonia and 4 patients placement, mean 3.5 ± 1.6 d (range: 2–10 d); length of postoperative hospital stay, mean 65.3 ± 34.2 mL (range: 20–220 mL); duration of chest tube

123 cases were as follows: duration of surgery, mean 113.4 ± 19.7 min (range: 20–150 min); blood loss, mean 65.3 ± 34.2 mL (range: 20–220 mL); duration of chest tube placement, mean 3.5 ± 1.6 d (range: 2–10 d); length of postoperative hospital stay, mean 6.8 ± 1.8 d (range: 5–15 d); and tumor diameter, mean 17.4 ± 11.4 mm (range: 5–60 mm). Surgical complications included one patient with pneumonia and 4 patients with prolonged air leak lasting > 5 d, which prolonged their hospital stays. No other complications were observed. Notably, there was no intraoperative massive hemorrhages, postoperative ICU stays, or 30-d mortalities.

Preoperative confirmation of anatomical variations

Owing to the complex anatomical variations of segmental vessels and bronchi, thoracoscopic segmentectomy requires more technical meticulousness than lobectomy. Preoperative 3D-CTBA images can clearly and vividly display the targeted structure and variations of vessels and bronchi (Figure 2). One example is variation of the right upper-lobe artery. In the case shown in Figure 2B, the A’a originated from the distal end of the A’, while the enlarged A’b coexisted with the proximal end of the A’. Care should be taken to protect the A1 when dealing with the A’b during the surgery. The 3D image in Figure 2D shows variations of the B’ and V’ in the right upper lobe. The posterior bronchus (B’) branched out separately, but the apical bronchus (B’a) and the anterior bronchus (B’b) originated from a common stem. When the B’ is resected, the surgeon often accidentally resects the B’a as well. In the same case, the right superior posterior pulmonary vein (V’b) merged into the right inferior pulmonary vein (RIPV). When the surgeon deals with the RIPV, the V’ can be mistakenly cut off altogether, leading to postoperative hemoptysis. Confirming anatomical variations before surgery can enable careful surgeon performance and better accuracy and security during the operation.

Identification of sufficient surgical margin

To reduce the risk of locoregional recurrence, preoperative planning is critical to securing a sufficient margin and minimizing anatomical resection of the targeted structure. The safety margin is defined as a sphere extending at least 2 cm outside the lesion or 2 cm greater than tumor size. When the cutting line is beyond the intersegmental plane, extended or combined segmentectomies are required, especially for intersegmental pulmonary nodules. The application of 3D-CTBA with a virtual 3D surgical margin helps the VATS surgeon determine accurate distances and positional relations among the tumor, bronchial trees, and intersegmental vessels. As shown in Figure 3, we precisely identified sufficient surgical margin after calculating the distance from the lesion to the predetermined cutting margin on the 3D-CTBA image. The extent of targeted lung parenchyma was labeled in yellow to facilitate adequate and precise resection.

Intraoperative navigation

Surgery was conducted according to the designed surgical procedure and with accurate intraoperative guidance by 3D-CTBA. As illustrated in Figure 4, we carefully performed segmentectomy of the RS’b, navigating by 3D-CTBA. A series of techniques were involved in the thoracoscopic segmentectomy, including location of pulmonary nodules, resection of the targeted vessels and bronchi, preservation of intersegmental veins, and identification of the intersegmental demarcation. Images 4A–D (respectively the Vc, A’b, B’b and Vb) indicate the resection sequence for the targeted vessels and bronchi. We defined the intersegmental demarcation (yellow dotted line) using the improved inflation–deflation method, with assistance from 3D-CTBA. Finally, surgeons precisely identified, separated, and dissected the targeted segment based on the cone-shaped principle.

Surgical outcomes and complications

As shown in Table 1, we observed no conversion from segmentectomy or lobectomy to open thoracotomy. The predominant pathology was adenocarcinoma, representing 98.2% of segmentectomy cases and 84.8% of lobectomy cases. Surgical results for all 123 cases were as follows: duration of surgery, mean 113.4 ± 19.7 min (range: 20–150 min); blood loss, mean 65.3 ± 34.2 mL (range: 20–220 mL); duration of chest tube placement, mean 3.5 ± 1.6 d (range: 2–10 d); length of postoperative hospital stay, mean 6.8 ± 1.8 d (range: 5–15 d); and tumor diameter, mean 17.4 ± 11.4 mm (range: 5–60 mm). Surgical complications included one patient with pneumonia and 4 patients with prolonged air leak lasting > 5 d, which prolonged their hospital stays. No other complications were observed. Notably, there was no intraoperative massive hemorrhages, postoperative ICU stays, or 30-d mortalities.

Table 2 shows the sites and VATS surgical procedures for the 123 patients who underwent segmentectomy and lobectomy. Anatomical resection of the right upper lobe (n = 20) was the most frequently performed lobectomy, followed by resection of the right lower (n = 12), left lower (n = 12), left upper (n = 12), and right middle (n = 80), and AIS (n = 21), invasive adenocarcinoma (IA; n = 80), and AIS (n = 11). All lymph nodes were pathological negative.
### Table 2 Sites of segmentectomy and lobectomy

<table>
<thead>
<tr>
<th>Site</th>
<th>Segmentectomy (n = 57)</th>
<th>Lobectomy (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS(^1+2)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>LS(^1+2)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LS(^1+2) a</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>LS(^1+2) b</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>LS(^1+2) c</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>LS(^1+2) + LS(^3)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>LS(^1+2) + LS(^4)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LS(^1) + LS(^2)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>LS(^1) + LS(^2) b</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lower lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS(^5)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>LS(^6)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LS(^5)+LS(^6)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Right lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS(^1) b</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>RS(^1) + RS(^1) a</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>RS(^1) + RS(^2)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>RS(^2)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>RS(^3)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>RS(^3) b</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>RS(^3) b(_a)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Middle lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS(^5)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lower lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS(^5)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>RS(^5) + RS(^5)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>RS(^5) a</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>RS(^6)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>RS(^6)+RS(^7)+RS(^9)+RS(^10)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Seg.: Segmentectomy; Subseg.: Subsegmentectomy; Sub-subseg.: Sub-subsegmentectomy.

**Figure 2** Presurgical confirmation of anatomical variations. Preoperative three-dimensional (3D) computed-tomography bronchography and angiography images can clearly and vividly display the targeted segmental structure and variations of vessels and bronchi. A: The bronchus of the right upper lobe is divided into the apical segmental bronchus (B₁), posterior segmental bronchus (B₂), and anterior segmental bronchus (B₃). The distance between the B₃a and B₃b of the anterior segmental bronchus is very great; B: The 3D image reveals the variations of the right upper-lobe artery: the A₃a originates from the distal end of the A₁, while the enlarged A₃b coexists with the proximal end of the A₁. Care should be taken to protect A₁ when dealing with the A₃b during the surgery; C: The segmental and subsegmental veins of the right upper lobe are labeled successively in the 3D image. There was no central vein, and the V₂a flowed into the apex vein (V₁) through the upper pulmonary hilum; D: The 3D image reveals the variations of the B₂ and V₂ in the right upper lobe. The B₂ branched out separately, but the A₃b and A₅ arose from a common stem. When the B₁ is resected, the surgeon often accidentally resects the B₂ as well. Additionally, the right upper posterior pulmonary vein (V₂) merged into the right inferior pulmonary vein (RIPV). When the surgeon deals with the right lower pulmonary vein, the V₂ could be mistakenly cut off altogether, leading to postoperative hemoptysis; E: The 3D image demonstrates the variation of the mediastinal lingual-segment artery (Med A₄+5) in the left upper lobe. The A₄b and A₅ of the left upper lingual-segment artery originated from the upper pulmonary trunk, while the A₄a originated from the interlobar-fissure artery separately. When left superior segmentectomy is performed, it is possible to cut off the A₄b and A₅ at the same time, resulting in decreased pulmonary blood flow to lingular-segment lung tissue and an imbalanced ventilation: Blood flow ratio.

10 lobes. The following segmentectomies were performed: single segmentectomy (n = 36), combined segmentectomy (n = 3), single subsegmentectomy (n = 9), segmentectomy combined with subsegmentectomy (n = 4), combined subsegmentectomy (n = 4), and sub-subsegmentectomy (n = 1). The top three single-segmentectomy sites were the RS₂ in the right upper lobe (n = 6), the RS₆ in the right lower lobe (n = 5), and the LS₄+₅ in the left upper lobe (n = 5).

**DISCUSSION**

This study analyzed the safety and feasibility of 3D-CTBA in performing VATS segmentectomy and lobectomy for primary lung cancers, including preoperative confirmation of anatomical variations, identification of sufficient surgical margin and intraoperative navigation. The purpose of our study is to assess the use of Mimics software in 3D-CTBA to help surgeons determine accurate distances and positional relations among the tumor, bronchial trees, and intersegmental vessels.

The higher frequency of diagnosis for small lung abnormalities elicits multiple questions about the optimal surgical approach in these patients, which has led to
Figure 3 Identification of sufficient surgical margin and preoperative surgery simulation. A: Chest computed tomography (CT) scan showed pure ground-glass opacity in the right upper lobe; B: We simulated surgery preoperatively, guided by a three-dimensional computed-tomography bronchography and angiography (3D-CTBA) images. The image showed that the targeted segmental structures needing to be successively resected were the V3c, A3b, B3b, and V3b; C: We precisely identified sufficient surgical margin after calculating the distance from the lesion to the predetermined cutting margin on the 3D-CTBA image. The safety margin was defined as a sphere extending at least 2 cm outside the lesion or 2 cm greater than the tumor size; D: The yellow area denotes the extent of targeted lung parenchyma RS3b. Afterward, we meticulously performed segmentectomy of the RS3b, as illustrated in Figure 4.

Segmentectomy's reaffirmation as an alternative to traditional lobectomy[10]. Many retrospective studies have shown that the efficacy of minimally invasive segmentectomy is consistent with that of lobectomy in early-stage lung cancer[11]. However, there are several concerns when surgeons balance the pros and cons of thoracoscopic segmentectomy. First, some retrospective reports have revealed that segmentectomy for lung cancer might have a higher rate of local recurrence than lobectomy[12,13]. In our study, preoperative segmentectomy simulation using 3D-CTBA enabled us to determine safe surgical margins and provide computer-aided support for surgical orientation and visualization to allow for more-secure execution. Another difficulty is segmental attribution of the tumor, especially when the nodule is near the boundary of pulmonary segments[14]. If the nodule is not accurately attributed to the targeted segment, incomplete excision and local recurrence can occur. The 3D reconstruction technique can be used to detect the exact location of the nodule and permit 3D visualization of segmental anatomy, like a “surgical map”[15]. After calculating the distance from the tumor to the predetermined cutting margin on 3D-CTBA images, thoracic surgeons can determine whether it is enough to resect a single segment or whether an extended or combined segmentectomy is required. Furthermore, the vascular architecture of pulmonary segments is remarkably complex and variable, and variations are often not detected by common 2D-CT. Nevertheless, as illustrated in Figure 2, any intrapulmonary vascular variation can be identified vividly on 3D images, which can help us plan precisely individualized surgeries for patients. With 3D-CTBA guidance, VATS segmentectomy in our study turned out to be as effective as lobectomy, with fewer complications.

The total mean tumor diameter in our study was 17.4 ± 11.4 mm (range: 5–60 mm). The mean tumor size was 10.5 ± 4.8 mm (range: 5–25 mm) in the segmentectomy group and 23.4 ± 12.1 mm (range: 8–60 mm) in the lobectomy groups. The majority of tumor appearance on CT was pGGN (55.3%) among all patients. The point of controversy is the best management policy for small tumors presenting as pure GGN and pGGN. First, many researchers worry that these small lesions are often overtreated. A recent article by Zhu et al[16] revealed that patients with micro-sized lung adenocarcinomas (≤ 1 cm in diameter) had better 5-year overall and disease-specific survival rates than those with small lung adenocarcinomas (1.1–2.0 cm in diameter), and that a sublobar surgical procedure was feasible. Second, it is difficult to palpate and pinpoint small nodules, some as small as a few millimeters in diameter, due to their nonsolid composition and deep location within the parenchyma. A variety of methods have been used to confirm the location of pulmonary nodules, such as methylene blue and CT-guided hookwire; with these methods, surgeons can solve the problem of wedge resection and lobectomy, rather than segmentectomy and subsegmentectomy[17]. Furthermore, surgeons are often confused by labyrinthine segment structures that cannot even be sufficiently mutually distinguished for segmentectomy or subsegmentectomy, resulting in high frequency of intraoperative and postoperative
Figure 4 Illustration of the precise surgical procedure navigated by three-dimensional computed-tomography bronchography and angiography. With the assistance of three-dimensional computed-tomography bronchography and angiography (3D-CTBA), we meticulously performed thoracoscopic segmentectomy of the RS\textsubscript{3b}. A series of techniques were involved in this procedure, including location of the pulmonary nodules, resection of targeted vessels and bronchi, preservation of intersegmental veins, and identification of the intersegmental demarcation. A–D: Images showing the resection sequence for the targeted vessels and bronchi, including the V\textsubscript{3c}, A\textsubscript{3b}, B\textsubscript{3b}, and V\textsubscript{3b}, respectively. The intersegmental demarcation (yellow dotted line) was defined by the improved inflation–deflation method, assisted by 3D-CTBA. The intersegmental veins V\textsubscript{1b} and V\textsubscript{3a} were carefully preserved. The surgeons precisely identified, separated, and dissected the targeted segment based on the cone-shaped principle; E, F: View of the hilum after RS\textsubscript{3b} removal reveals stumps of targeted vessels and bronchi, which was completely consistent with the preoperative 3D-CTBA images.

complications\cite{18}. With 3D-CTBA assistance, the surgeons at our center can ascertain pulmonary-segment anatomy and confirm the location of small nodules; therefore, a segmentectomy can be preoperatively planned and simulated, and then precisely navigated step by step during the operation. In our study, VATS segmentectomy was a meticulously performed procedure with fewer complications and better therapeutic benefit.

Despite the development of high-resolution 2D-CT, it is hard to achieve a vivid composition of the length, angle, dimensions, and direction of the targeted segment \cite{19}. The advent of 3D-CTBA provides more-accurate and detailed 3D imaging of the bronchi and pulmonary vessels of the regional anatomy, which consequently helps thoracic surgeons perfect anatomical orientation for VATS segmentectomy\cite{8,14,15}. The 3D-CTBA method is remarkable not only for its accuracy but also for its feasibility and visualization. Several studies have evaluated the feasibility of using different 3D-imaging software packages for thoracic surgery\cite{8,14,15,20-22}. She \textit{et al}\cite{15} and Wu \textit{et al}\cite{14} recommend DeepInsight software (Northeastern University, Shenyang, China). OsiriX is a powerful 3D reconstruction software with which surgeons can easily manipulate and process 2D-CT data into 3D images\cite{15}. Thanks to its stronger 3D reconstruction, Mimics provides a higher quality and completely realistic vision of the bronchi and the vessels, dramatically enhancing the dynamic range of 3D display and thus extending its ability to present images with a high degree of realism and a vivid stereoscopic feeling. This user-friendly software with its advanced image processing tools allows comprehensive information to be generated from images, meeting VATS requirements for surgeons worldwide.

With the application of 3D-CTBA, a series of thoracoscopic-surgery techniques have been gradually developed, such as location of pulmonary nodules, dissection of targeted vessels and bronchi, preservation of intersegmental veins, and identification of the intersegmental demarcation\cite{23}. First, we used CT-guided hookwire combined with 3D-CTBA images to precisely locate nodules before surgery. Combining different methods to accomplish this task is of vital importance, especially for small, deep
nodules or pure GGO. Notably, we encountered no intraoperative massive hemorrhage, thanks to our accurate determination of pulmonary vascular anatomy and variations. Additionally, we defined the intersegmental demarcation using the improved inflation-deflation method assisted by 3D-CTBA. The inflation-deflation interface was anatomically separated from the hilum to the distal region along the intersegmental veins and dissected using an electrotome and/or endoscopic staplers. The intersegmental vein and the inflation-deflation demarcation were identified as the markers of the intersegmental plane. Finally, with the help of Dr. Liang Chen, our institution explored the technique called “cone-shaped segmentectomy,” with which surgeons could precisely identify, separate, and dissect the targeted segment based on the cone-shaped principle.

There are several limitations to the utility of 3D-CTBA for surgical guidance. First, nearly all 3D-reconstruction software packages are designed for general business and industrial use, not specifically for medical applications, let alone thoracic surgery. Therefore, the 3D reconstruction procedure for pulmonary vessels and bronchi is not fully automated and is time consuming. Second, designing surgical procedures using 3D-CTBA technology depends on computer processing ability and the operational technique of the image software. The thoracic surgeon must not only cooperate with the radiologist, but also master radiological knowledge and ability. In addition, lesions are often detected by preoperative CT with the lung fully inflated, but during surgery the lung is often deflated. Understanding how preoperative conditions correlate with interoperative conditions requires significant experience and the ability to accurately identify anatomical structures. Furthermore, the size of the cohort in our study is a bit small, and more cases need to be collected in future. A final limitation is that we need more time to observe the postoperative recurrence and mortality rates in future studies. In the future, new high-quality software packages will hopefully facilitate the utility and diffusion of 3D technology among thoracic surgeons.

CONCLUSION

The advent of 3D-CTBA could dramatically change the VATS procedure for lung cancers, leading to a simpler, shorter, and more-accurate surgical process. The 3D-CTBA method enables the surgeon to visualize the anatomical relationship between the pulmonary nodule and the surrounding structure, which is valuable for a thoracoscopic-surgery strategy. The combination of VATS and 3D-CTBA worked in harmony in our study, and it also provided a new pattern of transition from the lesion-directed location of tumors to computer-aided surgery for the management of early-stage lung cancer.

ARTICLE HIGHLIGHTS

Research background

Performance of video-assisted thoracoscopic surgery (VATS) segmentectomy and lobectomy for primary lung cancer has currently increased. For small lung lesions, identification of the anatomical variation and intersegmental line is often difficult, and ensuring a sufficient surgical margin is more likely to be uncertain.

Research motivation

A lack of stereoscopic vision and the existence of anatomical variations create problems for surgeons during VATS, which can lead to unexpected complications.

Research objectives

The purpose of this study was to evaluate the therapeutic effect of VATS segmentectomy and lobectomy assisted by three-dimensional computed-tomography bronchography and angiography (3D-CTBA) on 123 patients.

Research methods

The 3D-CTBA during VATS segmentectomy and lobectomy was used for identifying the location of lesions, confirming anatomical variations, and securing the resection margins.
Research results
There was no intraoperative massive hemorrhages, postoperative intensive-care unit stays or 30-d mortalities. Three-dimensional navigation was performed to confirm the segmental structure, precisely cut off the targeted segment, and avoid intersegmental veins injury.

Research conclusions
The combination of VATS and 3D-CTBA worked in harmony in our study. This combination also demonstrated a new pattern of transition from lesion-directed location of tumors to computer-aided surgery for the management of small lung lesions.

Research perspectives
Intraoperative 3D-CTBA navigation could enable a more definitive VATS segmentectomy and lobectomy for early lung cancer.

ACKNOWLEDGEMENTS
We thank Dr. Liang Chen from Jiangsu Province Hospital for his helpful support and surgical skills.

REFERENCES


Wu YJ et al. Thoracoscopic segmentectomy and lobectomy assisted by assisted by 3D-CTBA

10.1016/j.ciresp.2017.01.005


Retrospective Study

Endoscopic ultrasound fine needle aspiration vs fine needle biopsy in solid lesions: A multi-center analysis

Diogo Turiani Hourneaux Moura, Thomas R McCarty, Pichamol Jirapinyo, Igor Braga Ribeiro, Galileu Ferreira Ayala Farias, Antonio Coutinho Madruga-Neto, Marvin Ryou, Christopher C Thompson

ORCID number: Diogo Turiani Hourneaux Moura 0000-0002-7446-0355; Thomas R McCarty 0000-0003-4517-5261; Pichamol Jirapinyo 0000-0001-5273-6851; Igor Braga Ribeiro 0000-0003-1844-8973; Galileu Ferreira Ayala Farias 0000-0003-0242-3691; Antonio Coutinho Madruga-Neto 0000-0003-2230-792X; Marvin Ryou 0000-0001-8120-6497; Christopher C Thompson 0000-0002-6105-5270.

Author contributions: de Moura DTH, Jirapinyo P and Ryou M contributed to study concept and design, manuscript preparation, critical revisions; McCarty TR contributed to statistical analyses, data interpretation, critical revisions; Ribeiro IB, Farias GFA and Madruga-Neto AC contributed to acquisition of data, statistical analyses, data interpretation; Thompson CC contributed to critical final review of manuscript/English review; all authors approve of the final version of the manuscript.

Institutional review board statement: The study was approved by the Research Ethics Committee from Partners Human Research (Protocol No. 2003P001665).

Informed consent statement: Diogo Turiani Hourneaux Moura, Igor Braga Ribeiro, Gastrointestinal Endoscopy Unit, University of Sao Paulo School of Medicine, Sao Paulo, SP 05403-010, Brazil

Diogo Turiani Hourneaux Moura, Thomas R McCarty, Pichamol Jirapinyo, Marvin Ryou, Christopher C Thompson, Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115, United States

Galileu Ferreira Ayala Farias, Antonio Coutinho Madruga-Neto, Division of Gastrointestinal Endoscopy, University of Sao Paulo Medical School, Sao Paulo, SP 01246-903, Brazil

Corresponding author: Igor Braga Ribeiro, MD, Associate Research Scientist, Surgeon, Gastrointestinal Endoscopy Unit, University of Sao Paulo School of Medicine, Av. Dr. Enéas de Carvalho Aguiar, 255 – Instituto Central - Prédio dos Ambulatórios, São Paulo, SP 05403-010, Brazil. igorbraga1@gmail.com

Abstract

BACKGROUND
While endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is considered a preferred technique for tissue sampling for solid lesions, fine needle biopsy (FNB) has recently been developed.

AIM
To compare the accuracy of FNB vs FNA in determining the diagnosis of solid lesions.

METHODS
A retrospective, multi-center study of EUS-guided tissue sampling using FNA vs FNB needles. Measured outcomes included diagnostic test characteristics (i.e., sensitivity, specificity, accuracy), use of rapid on-site evaluation (ROSE), and adverse events. Subgroup analyses were performed by type of lesion and diagnostic yield with or without ROSE. A multivariable logistic regression was also performed.

RESULTS
A total of 1168 patients with solid lesions (n = 468 FNA; n = 700 FNB) underwent EUS-guided sampling. Mean age was 65.02 ± 12.13 years. Overall, sensitivity, specificity and accuracy were superior for FNB vs FNA (84.70% vs 74.53%; 99.29%
Moura DTH et al. FNA vs FNB in solid lesions

Written informed consent was obtained from all patients.

Conflict-of-interest statement: Diogo Turiani Houngeaux de Moura, Thomas R McCarty, Pichamol Jirapinyo, Igor Braga Ribeiro, Galileu Ferreira Ayala Farias and Antonio Coutinho Madruga-Neto have nothing to disclose. Marvin Ryou reports other from Medtronic, other from GI Windows, other from EnteraSense, other from FujiFilm, other from Boston Scientific, grants from Olympus, other from Pentax, outside the submitted work. Christopher C Thompson reports personal fees from Medtronic, personal fees from Boston Scientific, grants from USGE Medical, grants from Apollo Endosurgery, grants from Olympus, outside the submitted work.

Data sharing statement: No additional data are available.

Country/Territory of origin: Brazil

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/License

INTRODUCTION

Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is a well-established technique for tissue acquisition of a variety of solid gastrointestinal tract lesions including pancreatic masses, subepithelial lesions, and mediastinal or abdominal lymphadenopathy. Despite being a well-described mode of tissue sampling, the diagnostic yield of FNA is highly variable ranging from 49% to 100% depending on the type of lesion[1-4]. Several factors including needle size and type, number of needle passes, lesion location and etiology, use of rapid-on-site evaluation (ROSE), and individual endoscopist experience may influence the diagnostic yield of the procedure. While several studies have shown some impact on diagnostic accuracy, careful focus to improve these characteristics has not consistently demonstrated improvement in diagnostic yield[5,6].

In addition to technical variables, EUS-guided FNA has specific limitations. Due to the small cellular sample provided by the FNA technique, multiple needle passes are often needed to establish a diagnosis. The operating characteristics of EUS-guided FNA are also incumbent upon the availability of a cytopathologist to perform ROSE, a highly technical resource that is not available in most centers[1,7]. Tissue architecture and morphology are often difficult to maintain with FNA samples – as a result, typically only providing specimen for cytological analysis. The reduced ability for histologic examination may reduce the diagnostic yield for lesions that require immunohistochemistry, immunophenotyping, or evaluation of histologic architecture such as lymphoma, metastatic lesions, and some subepithelial lesions[5,9]. Inflammatory processes may also adversely affect the diagnostic yield of FNA through associated cellular atypia resulting in false positive cytology[1,7,8].

Conflict of Interest: The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
To overcome limitations associated with EUS-guided FNA, core biopsy needles ([fine needle biopsy (FNB)]) have been developed, and are being increasingly utilized for tissue acquisition. These newer devices, which include reverse bevel needles, side-open needles, and fork-tip needles, are able to obtain both cytological aspirates and also histologic core samples.

Currently, core tissue samples obtained with these newer FNB needles may improve diagnostic yield and may potentially obviate the need for ROSE[1,5,7,8]. A meta-analysis have demonstrated FNB is a reliable diagnostic tool for solid lesions with similar diagnostic yield to FNA requiring fewer passes when compared to FNA without ROSE[10]. To date, there remains a paucity of high-quality data reporting FNB to be superior to FNA in terms of diagnostic yield and diagnostic accuracy in all types of solid lesions. Consequently, in 2017, the latest European Society of Gastrointestinal Endoscopy guidelines do not indicate that any needle type is superior or preferred for diagnostic sampling of solid lesions[11]. To better understand the comparative effectiveness of FNA vs FNB and possible advantages of EUS-guided FNB for solid lesions in daily clinical practice, we performed a large multi-center study to evaluate the diagnostic test characteristics of both sampling techniques with and without ROSE.

MATERIALS AND METHODS

This was a multi-center, retrospective study conducted at 5 hospitals in Massachusetts, United States (Brigham and Women’s Hospital, Massachusetts General Hospital, Brigham and Women’s Faulkner Hospital, Newton-Wellesley Hospital, and North Shore Medical Center) following the Standards for the Reporting of Diagnostic accuracy studies recommendations. All hospitals were affiliated with Partners Healthcare though each hospital utilizing different physician groups with varied EUS sampling practice protocols and diverse levels of experience. Ethical approval for the study was also provided the Research Ethics Committee from Partners Human Research (Protocol No. 2003P001665). Written informed consent was obtained from all patients.

Consecutive patients, age ≥ 18 years, were included if they had undergone EUS-guided tissue acquisition (FNA or FNB) of solid lesions from January 2016 to January 2019 were identified from a shared prospective registered. Data, including patient and lesion characteristics, were obtained from the electronic health record and registry dataset. Patient demographics, lesion characteristics, and procedure details, and diagnostic methods were recorded. Patient’s with incomplete reporting data or cases with more than one needle (i.e., FNA and FNB, or more needle sizes) used were excluded from this analysis.

Procedural technique

All EUS-guided tissue sampling procedures were performed with a linear array echoendoscope (Olympus GF-UCT180, Olympus, Center Valley, PA) under deep sedation with monitored anesthesia care. Anesthesia provider–administered sedation was performed for all included cases and EUS-guided FNA or FNB performed by experienced endosonographers or by gastroenterology fellows under direct, expert supervision. Several different needles were included, comprising of the 19G, 22G, and 25G FNA needles (Expect, Boston Scientific Corporation, Natick, MA or Echotip, Cook Medical, Winston-Salem, NC, United States or Beacon, Medtronic Corporation, Newton, MA) and 19G, 20G, 21G, 22G, and 25G FNB needles (Acquire, Boston Scientific Corporation, Natick, MA or SharkCore, Medtronic Corporation, Newton, MA or ProCore, Cook Medical, Winston-Salem, NC, United States). Both the decision regarding FNA vs FNB and needle size, were at the discretion of the endoscopist performing the procedure. Once the target lesion was properly identified on EUS, the lesion punctured was punctured with the needle under EUS guidance and a general fanning technique was performed. Given the inclusion of multiple hospitals and institutions, individual operator technique varied with respect to stylet use and slow-pull vs standard suction technique.

Samples obtained through FNA were transferred to slides. Each smear was made with slight pressure to avoid crushing artifacts, and the slides were placed in the 96% ethyl alcohol or fixed in the air. When possible, part of the specimens were placed in formalin solution for preparation of the cell-block. Samples obtained through FNB were fixed in buffered formalin and in selected cases, FNB specimens were prepared in slides using the touch imprint technique. Immunohistochemistry (IHC) staining was also performed for differential diagnosis of neoplastic and non-neoplastic lesions.
when needed, such as differential diagnosis of spindle cell lesions or in cases of lymphoma. In this study, ROSE was utilized to determine sample adequacy and assist in establishing a preliminary diagnosis. To perform ROSE, FNA specimens were expressed onto slides and then smeared for on-site preparation while FNB were prepared using the touch imprint technique. Per pass adequacy was determined based upon minimum number of passes required for the expert cytopathologist to provide a preliminary diagnosis. ROSE was performed in cases of EUS-guided FNA and FNB; however, this technique was not available for all cases. Therefore, separate analyses were performed to determine the impact of ROSE on diagnostic yield for EUS-guided FNA and FNB.

**Measured outcomes**

The primary outcome was the diagnostic yield [sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and accuracy] of EUS-guided FNA and FNB from cytologic or histologic analysis with and without IHC staining. Inconclusive specimen results were considered as non-neoplastic lesions as to not overestimate diagnostic yield. Secondary outcomes included the proportion of adequate cellularity for ROSE evaluation, median number of needle passes, diagnostic result from histologic (cell-block) and cytologic (slides) analysis, as well as adverse events related to the procedure. Surgical pathology of resected specimens was considered the golden standard method for comparison to EUS-guided FNA and FNA diagnostic performance. However, because most patients did not undergo surgery due to benign findings or advanced disease, patient follow-up for at least 6 months was also considered as the reference standard.

**Statistical analyses**

Baseline patient characteristics and procedure characteristics were summarized as means ± SD for continuous data and frequencies and proportions for categorical data. As diagnostic tests were performed on two independent groups of patients, a bivariate model was used to compute the pooled sensitivity and specificity, and diagnostic accuracy. Two-sample t-tests for binomial proportions were utilized. Continuous data were compared using the two-sample t-test or Wilcoxon rank-sum test and categorical data were compared using the Chi-square or Fisher’s exact test as appropriate. Statistical significance was defined as a $P < 0.05$.

Subgroup analyses were then performed to evaluate diagnostic yield of FNA and FNB for each location (pancreas subepithelial lesions, lymph nodes, and other lesion sites). Additional analyses were also performed to identify the diagnostic yield of FNA alone, FNA with ROSE, FNB alone, and FNB with ROSE. From this data, sensitivity, specificity, PPV, NPV, LR+, LR-, and accuracy were compared to determine if ROSE was beneficial. In effort to identify factors associated with diagnostic performance between FNA and FNB needle types, a multivariable logistic regression was performed with adjustment for clinically significant univariate findings as well as age, gender, number of passes, needle size, needle type, and application of ROSE, cell-block, and IHC. Results of the regression analysis were expressed as beta-coefficient ($\beta$) and odds ratio. Statistical analyses were performed using the Stata 15.0 software package (Stata Corp LP, College Station, TX).

**RESULTS**

**Baseline patient and lesion characteristics**

A total of 1168 consecutive patients (55.82% male) were enrolled in this study. Mean age of patients was 65.02 ± 12.13 years old with no difference between FNA and FNB cohorts ($P = 0.078$). There was no significant difference in gender between groups as well ($P = 0.098$). Of the 1168 patients that underwent EUS sampling, 40.07 ($n = 468$) underwent FNA with 59.93% ($n = 700$) undergoing sampling with FNB. Technical success occurred in all cases. A majority of lesions overall were non-pancreatic (50.14%) with further lesion characteristics highlighted in Table 1. Non-pancreatic lesions included lymph nodes and subepithelial lesions as well as other solid lesions such as hepatic masses and abdominal masses among others. FNB was more commonly performed for pancreatic lesions ($P < 0.001$) with FNA being the more common for non-pancreatic lesions ($P < 0.001$). Mean size of sampled lesions was 26.14 ± 13.643 mm with larger lesions in the FNB group (FNB 25.52 ± 13.65 vs FNA 22.10 ± 13.34; $P < 0.001$). Additional baseline characteristics for all included patients as well as
# Table 1 Baseline patient characteristics, lesion details, and sampling characteristics

<table>
<thead>
<tr>
<th>Results</th>
<th>Total</th>
<th>FNA</th>
<th>FNB</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>1168</td>
<td>468 (40.07)</td>
<td>700 (59.93)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.02 (12.29)</td>
<td>64.24 (11.59)</td>
<td>65.54 (12.72)</td>
<td>0.078</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.098</td>
</tr>
<tr>
<td>No. of males (%)</td>
<td>652 (55.82)</td>
<td>275 (58.76)</td>
<td>377 (52.86)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No. of females (%)</td>
<td>516 (44.18)</td>
<td>193 (41.24)</td>
<td>323 (47.14)</td>
<td></td>
</tr>
<tr>
<td>Lesion site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>574 (49.14)</td>
<td>194 (41.45)</td>
<td>380 (54.29)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-pancreatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node</td>
<td>209 (17.89)</td>
<td>108 (23.08)</td>
<td>101 (14.43)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Subepithelial</td>
<td>229 (19.61)</td>
<td>115 (24.57)</td>
<td>114 (16.28)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Other solid lesions</td>
<td>156 (13.36)</td>
<td>51 (10.90)</td>
<td>105 (15.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hepatic mass</td>
<td>48 (4.11)</td>
<td>18 (37.50)</td>
<td>30 (62.50)</td>
<td></td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>29 (2.48)</td>
<td>8 (27.59)</td>
<td>21 (72.41)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal wall thickening</td>
<td>20 (1.71)</td>
<td>6 (30.00)</td>
<td>14 (70.00)</td>
<td></td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>14 (0.43)</td>
<td>4 (28.57)</td>
<td>10 (71.43)</td>
<td></td>
</tr>
<tr>
<td>Peri-rectal mass</td>
<td>11 (0.94)</td>
<td>3 (27.37)</td>
<td>8 (72.73)</td>
<td></td>
</tr>
<tr>
<td>Common bile duct mass</td>
<td>9 (0.77)</td>
<td>5 (55.56)</td>
<td>4 (44.44)</td>
<td></td>
</tr>
<tr>
<td>Duodenal mass</td>
<td>6 (0.51)</td>
<td>1 (16.67)</td>
<td>5 (83.33)</td>
<td></td>
</tr>
<tr>
<td>Ampullary mass</td>
<td>6 (0.51)</td>
<td>1 (16.67)</td>
<td>5 (83.33)</td>
<td></td>
</tr>
<tr>
<td>Retropertoneal mass</td>
<td>5 (0.43)</td>
<td>1 (20.00)</td>
<td>4 (80.00)</td>
<td></td>
</tr>
<tr>
<td>Esophageal mass</td>
<td>3 (0.26)</td>
<td>0 (0.00)</td>
<td>3 (100.00)</td>
<td></td>
</tr>
<tr>
<td>Gastric bladder mass</td>
<td>3 (0.26)</td>
<td>2 (66.67)</td>
<td>1 (33.33)</td>
<td></td>
</tr>
<tr>
<td>Splenic mass</td>
<td>2 (0.17)</td>
<td>2 (100.00)</td>
<td>0 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Lesion size (mm)</td>
<td>24.16 (13.63)</td>
<td>22.10 (13.34)</td>
<td>25.52 (13.65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diagnostic sample approach</td>
<td></td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Transesophageal</td>
<td>124 (11.02)</td>
<td>63 (50.81)</td>
<td>61 (49.19)</td>
<td></td>
</tr>
<tr>
<td>Transgastric</td>
<td>589 (52.36)</td>
<td>235 (39.90)</td>
<td>354 (60.10)</td>
<td></td>
</tr>
<tr>
<td>Transduodenal</td>
<td>388 (34.49)</td>
<td>135 (34.79)</td>
<td>253 (65.21)</td>
<td></td>
</tr>
<tr>
<td>Transrectal</td>
<td>21 (1.87)</td>
<td>11 (52.38)</td>
<td>10 (47.62)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (0.26)</td>
<td>0 (0.00)</td>
<td>3 (100.00)</td>
<td></td>
</tr>
<tr>
<td>Needle size</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>19G</td>
<td>8 (0.69)</td>
<td>2 (0.43)</td>
<td>6 (0.86)</td>
<td></td>
</tr>
<tr>
<td>20G</td>
<td>7 (0.61)</td>
<td>0 (0.00)</td>
<td>7 (1.00)</td>
<td></td>
</tr>
<tr>
<td>21G</td>
<td>8 (0.69)</td>
<td>0 (0.00)</td>
<td>8 (1.15)</td>
<td></td>
</tr>
<tr>
<td>22G</td>
<td>644 (55.61)</td>
<td>216 (46.55)</td>
<td>428 (61.49)</td>
<td></td>
</tr>
<tr>
<td>25G</td>
<td>491 (42.40)</td>
<td>246 (53.02)</td>
<td>245 (55.20)</td>
<td></td>
</tr>
<tr>
<td>No. of passes</td>
<td>2.89 (1.51)</td>
<td>2.91 (1.61)</td>
<td>2.88 (1.45)</td>
<td>0.701</td>
</tr>
<tr>
<td>No. of samples with ROSE</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>377 (32.28)</td>
<td>182 (38.89)</td>
<td>195 (27.86)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>791 (67.72)</td>
<td>286 (61.11)</td>
<td>505 (72.14)</td>
<td></td>
</tr>
</tbody>
</table>
stratification by FNA or FNB cohort are demonstrated in Table 1.

**Needle and sampling characteristics**

Multiple needle sizes were utilized in this study, including 19G, 20G, 21G, 22G, and 25G. Of these, 22G and 25G were more commonly used (55.61% and 42.40%, respectively). A majority of FNA cases utilized a 25G needle while the 22G needle was most common for FNB \( (P < 0.001) \). Despite difference in needle type and size, there was no difference in number of needle passes between groups (FNA 2.91 ± 1.16 vs FNB 2.88 ± 1.45; \( P = 0.701 \)). More FNA obtained samples had ROSE performed \( (P < 0.001) \) with no difference in number of passes needle for ROSE adequacy between both groups \( (P = 0.474) \). Cell-block was more common among FNB samples (92.57% vs 78.21%; \( P < 0.001 \)) with similar number of passes required to achieve a conclusive diagnosis (3.09 ± 1.67 vs 2.90 ± 1.46; \( P = 0.067 \)). A further breakdown of needle type and sampling characteristics is illustrated in Table 1.

**Diagnostic characteristics of EUS-guided sampling**

Overall sensitivity, specificity, and accuracy for all lesions, regardless of sampling modality, was 81.02%, 97.92%, and 85.20%, respectively. Sensitivity, specificity, and accuracy of FNB outperformed diagnostic yield characteristics for FNA \( ([\text{sensitivity: } 84.70\% \text{ vs } 74.53\%; P < 0.001]), ([\text{specificity: } 99.29\% \text{ vs } 96.62\%; P < 0.001]), \text{ and } ([\text{accuracy: } 87.62\% \text{ vs } 81.55\%; P = 0.004])] \). One serious adverse event occurred in each group. Diagnostic characteristics were also stratified by type of lesions (pancreatic vs non-pancreatic lesions). For pancreatic lesions, total sensitivity, specificity, and accuracy of FNA and FNB combined was 87.96%, 97.59%, and 89.35%, respectively. Among pancreatic lesions, there was no difference in diagnostic yield between FNA vs FNB \( (P > 0.050) \). However, for non-pancreatic lesions, FNB resulted in a superior sensitivity (78.45% vs 63.29%; \( P < 0.001 \)), specificity (100.00% vs 96.52%; \( P < 0.001 \)) and accuracy (84.57% vs 77.29%; \( P = 0.023 \)). Complete diagnostic test characteristics are shown in Table 2.

**Diagnostic yield with and without ROSE**

A comparison between methods with and without ROSE was also performed (Tables 3 and 4). Table 3 shows the diagnostic yield of FNA and FNB with and without ROSE and Table 4 shows the statistical analysis of the comparison between methods. Overall, FNA with ROSE significantly improved the sensitivity, specificity, and accuracy of sampling when compared to FNA alone \( ([86.45\% \text{ vs } 63.19\%; P < 0.001]), ([100.00\% \text{ vs } 96.69\%; P = 0.014]), \text{ and } ([88.40\% \text{ vs } 77.56\%; P = 0.03]) \). When FNB alone was compared to FNA with ROSE, sensitivity, specificity, and accuracy were similar for both sampling modalities \( ([81.66\% \text{ vs } 86.45\%; P = 0.142]), ([100.00\% \text{ vs } 100.00\%; P = 1.00]), \text{ and } ([85.43\% \text{ vs } 88.40\%; P = 0.320]) \).

**Multivariate logistic regression**

Multivariate analysis was then performed controlling for age, gender, number of passes, needle type, needle size, application of ROSE, and application of cell-block, on accuracy. Based upon the results of this multivariate logistic regression, and controlled for the variables above, there was no significant predictor for better accuracy.
Table 2 Summary of diagnostic results

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>FNA</th>
<th>FNB</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>81.02% (95% CI 78.27 to 83.56)</td>
<td>74.53% (95% CI 69.37 to 79.23)</td>
<td>84.70% (95% CI 81.45 to 87.57)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.92% (95% CI 95.54 to 99.23)</td>
<td>96.62% (95% CI 92.29 to 98.89)</td>
<td>99.29% (95% CI 96.11 to 99.98)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>0.19 (95% CI 0.17 to 0.22)</td>
<td>0.26 (95% CI 0.22 to 0.32)</td>
<td>0.15 (95% CI 0.13 to 0.19)</td>
<td>0.676</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>99.17% (95% CI 98.18 to 99.62)</td>
<td>97.93% (95% CI 95.23 to 99.12)</td>
<td>99.79% (95% CI 98.54 to 99.97)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>62.89% (95% CI 59.63 to 66.04)</td>
<td>63.84% (95% CI 59.34 to 68.11)</td>
<td>61.95% (95% CI 57.26 to 66.43)</td>
<td>0.459</td>
</tr>
<tr>
<td>Accuracy</td>
<td>85.20% (95% CI 83.03 to 87.19)</td>
<td>81.55% (95% CI 77.72 to 84.96)</td>
<td>87.62% (95% CI 84.96 to 89.97)</td>
<td>0.004</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>2 (0.17)</td>
<td>1 (0.21)</td>
<td>1 (0.14)</td>
<td>0.775</td>
</tr>
<tr>
<td><strong>Pancreatic lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87.96% (95% CI 84.74 to 90.71)</td>
<td>85.62% (95% CI 79.22 to 90.66)</td>
<td>89.09% (95% CI 85.22 to 92.24)</td>
<td>0.229</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.59% (95% CI 91.57 to 99.71)</td>
<td>96.88% (95% CI 93.78 to 99.92)</td>
<td>98.04% (95% CI 89.55 to 99.95)</td>
<td>0.387</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>36.50% (95% CI 9.38 to 143.58)</td>
<td>27.40% (95% CI 10.88 to 188.81)</td>
<td>45.44% (95% CI 31.62 to 61.15)</td>
<td>0.714</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.12 (95% CI 0.10 to 0.16)</td>
<td>0.15 (95% CI 0.10 to 0.22)</td>
<td>0.11 (95% CI 0.08 to 0.15)</td>
<td>0.253</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>99.54% (95% CI 98.21 to 99.88)</td>
<td>99.28% (95% CI 95.21 to 99.92)</td>
<td>99.66% (95% CI 97.69 to 99.95)</td>
<td>0.529</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>57.86% (95% CI 51.88 to 63.61)</td>
<td>57.41% (95% CI 47.88 to 66.41)</td>
<td>58.14% (95% CI 50.44 to 65.46)</td>
<td>0.867</td>
</tr>
<tr>
<td>Accuracy</td>
<td>89.35% (95% CI 86.54 to 91.76)</td>
<td>87.50% (95% CI 81.97 to 91.82)</td>
<td>90.29% (95% CI 86.86 to 93.07)</td>
<td>0.307</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 (0.17)</td>
<td>0 (0.00)</td>
<td>1 (0.26)</td>
<td>0.821</td>
</tr>
<tr>
<td><strong>Non-pancreatic lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>72.31% (95% CI 67.58 to 76.69)</td>
<td>63.29% (95% CI 55.27 to 70.81)</td>
<td>78.45% (95% CI 72.59 to 83.56)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.07% (95% CI 95.13 to 99.47)</td>
<td>96.52% (95% CI 91.33 to 99.04)</td>
<td>100.00% (95% CI 96.07 to 100.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>37.42% (95% CI 14.15 to 98.95)</td>
<td>18.20% (95% CI 6.90 to 48.01)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.28% (95% CI 0.24 to 0.33)</td>
<td>0.38% (95% CI 0.31 to 0.47)</td>
<td>0.22% (95% CI 0.17 to 0.28)</td>
<td>0.719</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>98.60% (95% CI 96.38 to 99.47)</td>
<td>96.15% (95% CI 90.45 to 98.51)</td>
<td>100.00%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>65.27% (95% CI 61.53 to 68.84)</td>
<td>65.68% (95% CI 60.86 to 70.20)</td>
<td>64.79% (95% CI 59.01 to 70.17)</td>
<td>0.820</td>
</tr>
<tr>
<td>Accuracy</td>
<td>81.24% (95% CI 77.87 to 84.29)</td>
<td>77.29% (95% CI 71.85 to 82.12)</td>
<td>84.57% (95% CI 80.17 to 88.32)</td>
<td>0.023</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 (0.16)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0.321</td>
</tr>
</tbody>
</table>

FNA: Fine needle aspiration; FNB: Fine needle biopsy; ROSE: Rapid on-site evaluation.

DISCUSSION

This is the first study to compare FNA and FNB with and without ROSE in solid lesions. Additionally, in this large, multi-center study, we compared EUS-FNA and EUS-FNB in many respects. EUS-FNB was superior to EUS-FNA regarding sensitivity, specificity, and accuracy and allowed for more cell-block diagnosis. However, EUS-FNB was comparable to EUS-FNA regarding number of passes required for ROSE and cell-block evaluation. The addition of ROSE to EUS-FNA provided better accuracy as compared to FNA alone and similar accuracy compared to FNB alone. The addition of ROSE to EUS-FNB did not improve the diagnostic accuracy of FNB alone for all solid lesions, suggesting that EUS-FNB may eliminate the need for ROSE in EUS-guided tissue sampling.

EUS-FNA of solid lesions is a safe procedure, associated with high diagnostic accuracy, usually above 85%, and typically better when ROSE is available[6,10]. However, the diagnostic accuracy of EUS-FNA with cytology is insufficient to verify cellular arrangement and tissue architecture. Procurement of histological samples that yield an adequate amount of tissue suitable for IHC staining is pivotal for personalized management of some lesions, such as metastatic lesions, gastrointestinal stromal...
### Table 3 Comparison between methods with and without rapid on-site evaluation

<table>
<thead>
<tr>
<th></th>
<th>FNA alone</th>
<th>FNA with ROSE</th>
<th>FNB alone</th>
<th>FNB with ROSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>63.19% (95%CI 55.29 to 70.60)</td>
<td>86.45% (95%CI 80.04 to 91.41)</td>
<td>81.66% (95%CI 77.50 to 85.34)</td>
<td>82.97% (95%CI 76.70 to 88.12)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>96.69% (95%CI 91.73 to 99.06)</td>
<td>100.00% (95%CI 98.77 to 100.00)</td>
<td>100.00% (95%CI 95.04 to 100.00)</td>
<td>100.00% (95%CI 96.04 to 100.00)</td>
</tr>
<tr>
<td><strong>Positive likelihood ratio</strong></td>
<td>19.12 (95%CI 7.24 to 50.46)</td>
<td>239.82 (95%CI 12.76 to 632.37)</td>
<td>0.19 (95%CI 0.15 to 0.23)</td>
<td>0.17 (95%CI 0.12 to 0.23)</td>
</tr>
<tr>
<td><strong>Negative likelihood ratio</strong></td>
<td>0.38 (95%CI 0.31 to 0.47)</td>
<td>0.14 (95%CI 0.09 to 0.20)</td>
<td>0.19 (95%CI 0.15 to 0.23)</td>
<td>0.17 (95%CI 0.12 to 0.23)</td>
</tr>
<tr>
<td><strong>Positive predictive value</strong></td>
<td>96.26% (95%CI 90.70 to 98.55)</td>
<td>100.00%</td>
<td>99.69% (95%CI 97.88 to 99.96)</td>
<td>100.00%</td>
</tr>
<tr>
<td><strong>Negative predictive value</strong></td>
<td>66.10% (95%CI 61.40 to 70.51)</td>
<td>55.32% (95%CI 45.41 to 64.82)</td>
<td>59.89% (95%CI 52.81 to 64.77)</td>
<td>29.55% (95%CI 23.33 to 36.62)</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>77.46% (95%CI 72.16 to 82.19)</td>
<td>88.40% (95%CI 82.06 to 88.39)</td>
<td>85.43% (95%CI 78.20 to 88.94)</td>
<td>84.10% (95%CI 78.20 to 88.94)</td>
</tr>
</tbody>
</table>

FNA: Fine needle aspiration; FNB: Fine needle biopsy; ROSE: Rapid on-site evaluation.

tumors, lymphomas, and other uncommon lesions[7,9]. The limitation in achieving diagnosis using EUS-FNA is the pauci-cellular nature of the aspirate with a significant proportion of the collected tissue being distorted or consumed during automated processing and sectioning[7]. In our study, cell-block analysis was possible in 78.21% of patients after FNA and in 92.57% after FNB (P < 0.001). Our results are similar to a previous systematic review and meta-analysis including eight randomized controlled trials that compared these techniques[12].

In our study, technical success was reported in all patients, similar to several studies evaluating FNB needles[13-15]. These results demonstrate that FNB can be easily performed in any location, unlike the first-generation FNB device (Tru-cut)[16]. Most studies comparing FNA and FNB have demonstrated that FNB typically requires fewer needle passes to achieve adequate sampling for ROSE and cell-block[12,13]. A lower number of passes may be translated into shorter procedure time, less risk of adverse events, and more operational efficiency for both endoscopy and cytopathology units. However, different from previous studies, in our analysis the number of passes required to achieve adequate samples for ROSE (FNA: 3.32 ± 1.74 vs FNB: 3.41 ± 1.73; P > 0.05) and cell-block (FNA: 3.09 ± 1.67 vs FNB: 2.90 ± 1.46; P > 0.05) were similar between both techniques. Similar to our study, Bang et al[17] also showed no significant difference in mean number of passes required to establish a diagnosis in a randomized controlled trial. Nevertheless, our study illustrated FNB enables a diagnostic yield of more than 90% for cell-block assessment (FNA: 78.21% vs FNB: 92.57%; P < 0.001). Additionally, EUS-FNA with ROSE presented similar results to EUS-FNB alone. Similar to our results, a previous meta-analysis also showed that EUS-FNB without ROSE provides a similar diagnostic yield than EUS-FNA with ROSE[10]. Uniquely, in the subgroup analysis we demonstrated that FNB with ROSE is similar to FNB alone, suggesting that this technique may eliminate the need for ROSE.
Different from most studies available in the literature, we analyzed the sensitivity, specificity, LR+, LR-, PPV, NPV, and accuracy of EUS-FNA compared to EUS-FNB in all solid lesions\cite{8,13-15}. EUS-FNB had a better sensitivity (84.70% vs 74.53%), specificity (99.29% vs 96.62%), and accuracy (87.62% vs 81.55%) when compared to EUS-FNA with statistical significance. Our results are similar to a recent large randomized trial comparing EUS-FNA and EUS-FNB in solid lesions including 408 patients (249 pancreatic lesion and 159 non-pancreatic masses)\cite{14}.

Interestingly, when we compare pancreatic and non-pancreatic lesions, a statistical difference was found only for the non-pancreatic lesions group. In the pancreatic group, despite superiority of FNB when compared to FNA regarding sensitivity (89.09% vs 85.62%), specificity (98.04% vs 96.88%), and accuracy (90.29% vs 87.50%), no statistical difference was found. The similar diagnostic yield between both techniques in pancreatic lesions reported in our study is compatible with previous studies, including a systematic review and meta-analysis based upon 27 randomized controlled trials\cite{18}. These results may be related to the fact that both procedures have a high accuracy rate, and thus even an even larger number of patients (i.e., higher power) may be necessary to determine if FNB is superior.

Studies diverge on consideration of an inconclusive (non-diagnostic) result as benign or the decision to exclude this finding from the analysis. This fact is related to the heterogeneity of the previous results published in the literature\cite{14,19,20}. When excluding inconclusive results, an increase in accuracy is observed, though this may be falsely elevated. In this analysis, we chose to be more rigorous and considered inconclusive results as benign lesions as to not overestimate diagnostic accuracy. As expected from sampling diagnostic modalities, the specificity and PPV were high in both techniques, showing that a positive result for a malignant lesion is very reliable. However, in both groups the sensitivity and NPV were low, and thus a negative result cannot entirely exclude a neoplastic lesion.

In our study, we also performed a multivariate analysis to find an association between several variables, including age, gender, needle type, needle size, use of ROSE, and cell-block assessment on diagnostic accuracy. In our analysis, no predictors were associated with better accuracy. Different from our study, in a multivariable logistic regression of a series including both pancreatic and non-pancreatic solid lesions, FNB and lesion size were associated with the need to perform only one pass to achieve onsite diagnostic adequacy and were associated with procurement of diagnostically adequate histological specimens for offsite assessment\cite{7}.

The safety of EUS-tissue sampling is well established, and few adverse events are encountered in the literature. Severe adverse events are especially rare\cite{15,17}. The safety profile of FNB was comparable to that of FNA, with only one adverse event encountered in each cohort. The adverse event occurred after an FNB procedure for suspected neuroendocrine tumor with active acute pancreatitis, which is a contraindication for the procedure. After the procedure, the patient clinically deteriorated, and passed away. We believe that this adverse event was not directly related to FNB as a technique, with any tissue sampling technique possessing the potential to cause this adverse event. Therefore, we do not recommend EUS-tissue sampling in patients with acute pancreatitis. The adverse event in the FNA group was a minor hemorrhage after subepithelial lesions sampling treated with epinephrine injection. In the literature, several studies showed no adverse events related to EUS-FNA or EUS-FNB in the diagnosis of solid lesions\cite{9,13,14}.

Despite being the largest study to date to evaluate the role of EUS-FNA and EUS-FNB with and without ROSE in solid lesions, we recognize there are some limitations to our study. This was a retrospective study with the inherent limitations expected with such a design, including potential selection bias, lack of randomization, loss-to-follow-up, and potential for cofounders. This selection bias may be seen in the baseline differences between patients that underwent FNA vs FNB; however, a logistic regression was performed in an attempt to control for these factors. Although none of the patients with benign disease demonstrated disease progression at follow-up, we could not obtain further tissue results for ethical concerns. Furthermore, in effort to simulate clinical practice, multiple available needles sizes were used and thus we cannot discount heterogeneity of our results or fail to acknowledge inter-operator variability using these different needle sizes. Reassuringly, a previous meta-analysis including only high-quality randomized controlled trials, did not show significant difference between varied needles sizes\cite{6}. Procedural costs were not compared between the two cohorts in our study. However, recently a randomized trial showed that the strategy of EUS-FNB was cost saving compared to EUS-FNA over a wide range of cost and outcome probabilities\cite{8}. 

CONCLUSION

In summary, EUS-FNB is superior to EUS-FNA in the diagnosis of solid lesions and allows more cell-block evaluation, with similar number of passes required to achieve an adequate sample. EUS-FNA with ROSE and EUS-FNB with ROSE were found to have a similar sensitivity to EUS-FNB alone.

ARTICLE HIGHLIGHTS

Research background
While endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is considered a preferred technique for tissue sampling for solid lesions, fine needle biopsy (FNB) has recently been developed with the capability of tissue extraction for histological evaluation.

Research motivation
To better understand the comparative effectiveness of FNA vs FNB and possible advantages of EUS-guided FNB for solid lesions in daily clinical practice.

Research objectives
Evaluate the diagnostic test characteristics of EUS-FNA and EUS-FNB sampling techniques with and without rapid on-site evaluation (ROSE).

Research methods
Multi-center, retrospective study conducted at 5 hospitals in Massachusetts, United States following the Standards for the Reporting of Diagnostic accuracy studies recommendations.

Research results
A total of 1168 patients with solid lesions underwent EUS-guided sampling. Overall, sensitivity, specificity and accuracy were superior for FNB vs FNA. On subgroup analyses, sensitivity, specificity, and accuracy of FNB alone were similar to FNA + ROSE. There were no difference in diagnostic yield of FNB alone vs FNB + ROSE.

Research conclusions
FNB is superior to FNA with equivalent diagnostic test characteristics compared to FNA + ROSE in the diagnosis of non-pancreatic solid lesions.

Research perspectives
Our results suggest that EUS-FNB may eliminate the need of ROSE and should be employed as a first-line method in the diagnosis of solid lesions.

REFERENCES


Resection of bilateral occipital lobe lesions during a single operation as a treatment for bilateral occipital lobe epilepsy

Yan-En Lyu, Xiao-Fei Xu, Shuang Dai, Min Feng, Shao-Ping Shen, Guo-Zhen Zhang, Hong-Yan Ju, Yao Wang, Xiao-Bo Dong, Bin Xu

Abstract

BACKGROUND
Neurosurgical treatment of severe bilateral occipital lobe epilepsy usually involves two operations several mos apart.

AIM
To evaluate surgical resection of bilateral occipital lobe lesions during a single operation as a treatment for bilateral occipital lobe epilepsy.

METHODS
This retrospective case series included patients with drug-refractory bilateral occipital lobe epilepsy treated surgically between March 2006 and November 2015.

RESULTS
Preoperative evaluation included scalp video-electroencephalography (EEG), magnetic resonance imaging, and PET-CT. During surgery (bilateral occipital craniotomy), epileptic foci and important functional areas were identified by EEG (intracranial cortical electrodes) and cortical functional mapping, respectively. Patients were followed up for at least 5 years to evaluate treatment outcome (Engel grade) and visual function. The 20 patients (12 males) were aged 4-30 years (median age, 12 years). Time since onset was 3-20 years (median, 8 years), and episode frequency was 4-270/mo (median, 15/mo). Common manifestations were
INTRODUCTION

Occipital lobe epilepsy[1] is an uncommon form of epilepsy that accounts for only 2%-13% of cases of symptomatic focal epilepsy[1-6]. The symptoms of occipital lobe epilepsy are mainly visual and oculomotor manifestations and include visual illusion, elementary visual hallucinations, blinking, a sensation of eye movement, dizziness, ictal blindness, and contralateral eye and head deviation[1,5-9]. The diagnosis of occipital lobe epilepsy can be challenging because of the rapid spread of the seizure to the frontal, temporal and parietal lobes and the midbrain tegmentum[5, 6,10]. Therefore, achieving a definitive diagnosis generally requires the use of scalp electroencephalograms (EEGs), magnetic resonance imaging (MRI), fluoro-deoxy-glucose positron emission tomography (FDG-PET), single-photon emission computed tomography (SPECT), and/or video-EEG monitoring with intracranial electrodes[4,7,9, 11-13].

Although pharmacologic therapies are available for focal epilepsy[14], some cases are resistant to drugs and require neurosurgical intervention[7,15-18]. A small number of reports have described the surgical management of intractable occipital lobe epilepsy, and the techniques used included lesionectomy, corticectomy, and lobectomy[7-9,15,17,19-29]. However, the majority of previous clinical investigations have focused on patients with unilateral occipital lobe epilepsy, and there are very few published studies describing the surgical management of patients with bilateral occipital lobe epilepsy[30]. Generally, the neurosurgical management of bilateral occipital lobe epilepsy involves resection of the lesion on one side, a 6 mo recovery period, and finally resection of the lesion on the other side. Although this approach is considered relatively safe, it requires two surgical procedures spaced 6 mo apart. The surgical treatment of bilateral occipital lobe epilepsy during a single operation would have several potential advantages, such as a reduced number of surgeries and hospitalizations, a shorter treatment time, lower treatment costs, and decreased psycho-
logical stress for the patients and their families. However, to the best of our knowledge, no previous studies have reported the treatment of bilateral occipital lobe epilepsy using a single surgical procedure.

MATERIALS AND METHODS

Study design and patients

This retrospective case series included 20 patients with bilateral occipital lobe epilepsy refractory to medical therapy who were treated surgically at the Epilepsy Center, General Hospital of the Beijing Military Command Region and the Epilepsy Center, Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine between March 2006 and November 2015. The inclusion criteria were: (1) A diagnosis of bilateral occipital lobe epilepsy based on the medical history, seizure characteristics, EEG, and imaging investigations; (2) Frequent occurrence of seizures that severely affected the quality of life; (3) Seizures refractory to drug therapy; and (4) Bilateral occipital lobe lesions were treated surgically during a single operation. The diagnosis of bilateral occipital lobe epilepsy was based on the following features: (1) Scalp video-EEG monitoring showed abnormal firing in both sides of the occipital lobe, with some seizures originating from the left side and other episodes originating from the right side; (2) Imaging examinations showed abnormalities of the bilateral occipital lobe (a negative result did not exclude bilateral occipital lobe epilepsy); and (3) The form of the episode was related to the side of the occipital lobe in which it originated, and the seizure side was sometimes on the left and sometimes on the right. The exclusion criteria were: (1) A definitive diagnosis of bilateral occipital lobe epilepsy could not be made; (2) Epileptogenic lesions outside the occipital lobe; (3) Infrequent occurrence of episodes that did not merit surgery; and (4) Other serious diseases or contraindications to surgery.

The ethics committee of Beijing university of Chinese medicine dongzhimen hospital approved this study. All patients provided written consent for surgery after being informed of the potential benefits and risks. Informed consent for inclusion was waived because the analysis was retrospective.

Baseline demographic and clinical characteristics

Preoperative evaluation: All patients underwent scalp video-EEG for 48-170 h to record abnormal discharges during the interictal period as well as more than five seizures. The patients were also evaluated using MRI (3D thin-layer T1-weighted and T2-weighted scanning and T2-FLAIR imaging). In addition, PET-CT was used for individual patients with an unclear diagnosis based on video-EEG and MRI.

Neurosurgery: All operations were presided over by the same senior chief physician who had many years of clinical neurosurgery experience, including the resection of epileptogenic lesions under video-EEG monitoring. Surgery for each patient was planned and carried out by a multi-disciplinary team of doctors and nurses. The bilateral occipital lobe lesions were resected during a single surgical procedure in all patients.

First, a bilateral occipital craniotomy was performed (Figure 1A and B). Intracranial cortical electrodes (AD-Tech Medical, Oak Creek, WI, United States) were placed on the surface of the bilateral occipital lobe (Figure 1C), and EEG monitoring (128-channel video EEG monitoring system; Nicolet, Natus Medical Incorporated, United States) was carried out to determine the epileptic foci. Next, the important functional areas that needed protecting during surgery were identified by cortical functional mapping, and the scope of the resection and the areas to be protected were determined. Then the lesions in the bilateral occipital lobe were surgically resected (Figure 1D). During surgery, particular attention was paid to the following: (1) To ensure full exposure of the bilateral occipital lobe, the lower level of the incision was extended to reach the level of the transverse sinus so that the sinus confluence and part of the transverse sinus were exposed; (2) The bone flap was removed without a midline bone bridge; (3) Great care was taken to avoid severe bleeding caused by injury to the sagittal sinus, sinus confluence, and transverse sinuses; (4) The locations and numbers of cortical electrodes were determined according to the results of preoperative EEG monitoring to avoid the omission of epileptogenic foci; and (5) The location and scope of the resection were determined according to the results of cortical EEG monitoring and cortical function mapping to optimize complete resection of the epileptogenic lesions while protecting brain function to the maximal extent. In general, the resected area of...
the occipital lobe could be extended to the temporo-occipital junction laterally, to the posterior part of the parietal lobe, and to below the precuneus. When the occipital lobe showed definite morphologic changes, the epileptogenic foci surrounding the lesions were removed as much as possible. If the lesion was located outside the calcarine fissure, individually tailored cortical resection was used to minimize injury to the visual cortex.

Follow-up and outcome measures
All patients underwent reexamination and postoperative follow-up at least once each year for a minimum of 5 years to evaluate the effects of treatment on the incidence of seizures and visual function (including visual fields). The outcome of epilepsy surgery was graded I-IV according to the Engel classification[31]. Visual function in cooperative patients was assessed by clinical examination of vision and the visual fields. The visual function of patients who could not cooperate with a full vision examination, for example, due to young age, was assessed from their behavioral activity and information provided by the parents. In addition, any other notable changes in physical or psychological status during follow-up were recorded.

Statistical analysis
A descriptive statistical approach was used for the analysis, which was performed using SPSS 22.0 (IBM Corp., Armonk, NY, United States). Data are presented as n (%) or median (range).

RESULTS
Baseline clinical characteristics of the study participants
The baseline clinical characteristics of the 20 patients (12 males) with bilateral occipital lobe epilepsy included in the study are presented in Table 1. The patients were aged 4-30 years with a median age of 12 years. The time since disease onset ranged from 3-20 years, and all patients had been experiencing frequent episodes of drug-refractory epilepsy (median frequency of 15 episodes per mo). The most common clinical
Table 1 Baseline clinical characteristics of the 20 patients treated surgically for bilateral occipital lobe epilepsy

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (60.0)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td>Age (yr), median (range)</td>
<td>12 (4-30)</td>
</tr>
<tr>
<td>Age at disease onset (yr), median (range)</td>
<td>5 (1-11)</td>
</tr>
<tr>
<td>Frequency of epilepsy (episodes per mo), median (range)</td>
<td>15 (4-270)</td>
</tr>
<tr>
<td>Time since disease onset (yr), median (range)</td>
<td>8 (3-20)</td>
</tr>
<tr>
<td>Pathology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Cortical dysplasia</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Multiple nodular sclerosis</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Lobe atrophy</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Clinical manifestations, n (%)</td>
<td></td>
</tr>
<tr>
<td>Elementary visual hallucinations</td>
<td>13 (65.0)</td>
</tr>
<tr>
<td>Flashing lights</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>Field defect</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>Blindness</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Visual illusion</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Blinking</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Sensation of eye movement</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Deja vu</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fear</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Epigastric rising sensation</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

manifestations (see Table 1) were elementary visual hallucinations (13/20, 65.0%), flashing lights (6/20, 30.0%), blurred vision (4/20, 20.0%) and visual field defects (4/20, 20.0%).

**Outcome of epilepsy surgery assessed using the Engel classification**

All patients underwent resection of bilateral occipital lesions, and the hospitalization time ranged from 15-20 d. The surgical outcomes are presented in Table 2. The vast majority of patients were seizure-free (Engel grade I) in the postoperative period (18/20, 90.0%) and at 1 year (18/20, 90.0%), 3 years (17/20, 85.0%) and ≥ 5 years (17/20, 85.0%). Importantly, no patients were classified as Engel grade IV (no worthwhile improvement) at any of the follow-up time points.

**Postoperative changes in visual function**

Visual field changes after surgery are summarized in Table 3. After the operation, 13 patients (65.0%) showed no change in visual function, three patients (15.0%) developed a new visual field defect, and four patients (20.0%) exhibited worsening of a defect that had been present preoperatively. Four patients (20.0%) had partial visual
Table 2 Surgical outcomes assessed using the Engel classification

<table>
<thead>
<tr>
<th>Follow-up time point and outcome</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative period</td>
<td></td>
</tr>
<tr>
<td>Engel grade I</td>
<td>18 (90.0)</td>
</tr>
<tr>
<td>Engel grade II</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Engel grade III</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>1 yr</td>
<td></td>
</tr>
<tr>
<td>Engel grade I</td>
<td>18 (90.0)</td>
</tr>
<tr>
<td>Engel grade II</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Engel grade III</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>3 yr</td>
<td></td>
</tr>
<tr>
<td>Engel grade I</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Engel grade II</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Engel grade III</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>5 yr or more</td>
<td></td>
</tr>
<tr>
<td>Engel grade I</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Engel grade II</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Engel grade III</td>
<td>1 (5.0)</td>
</tr>
</tbody>
</table>

Table 3 Visual field changes after surgery

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual field before surgery</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>Quadrantanopia</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Hemianopsia</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other types of defect</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>Visual field change after surgery</td>
<td></td>
</tr>
<tr>
<td>Normal to normal</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Normal to defect</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Worsening of defect</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>No change in defect</td>
<td>7 (35.0)</td>
</tr>
</tbody>
</table>

field loss or increased visual field loss after surgery, and one patient (5.0%) experienced temporary postoperative blindness with the recovery of visual acuity within the subsequent mo. One patient (5.0%) had severe visual impairment before surgery that did not change postoperatively. Two patients (10.0%) showed a notable improvement in visual acuity after surgery. One was a 10-year-old boy who complained of dizziness when wearing glasses to correct his vision before surgery; the patient no longer needed glasses after surgery, which had the added benefit of avoiding the occurrence of dizzy spells. The other was a 16-year-old girl with poor vision preoperatively; after surgery, her vision improved sufficiently such that she no longer needed assistance or the use of handrails to walk or ascend/descend stairs.

Other postoperative changes
A 7-year-old boy with facial sebaceous adenoma exhibited a substantial reduction in lesion number and size after surgery. In addition, a 30-year-old male had postoperative resolution of multiple psoriatic lesions that had been resistant to medical treatment for many years.
Case 1: A 15-year-old male patient had a history of asphyxia at birth associated with cyanosis and lethargy on the fourth day after birth. An episode of right limb rigidity developed on day 55 after birth, but this resolved after treatment. Absence seizures began to occur when the patient was 4 years old, and at the age of 6 years, the patient started to experience episodes approximately once per mo in which the eyeballs and head turned to the left, and the right limbs twitched. The patient was given various medications, including carbamazepine and dianxianling, but the seizures were not fully controlled. One mo before admission, the patient experienced an episode in which he was described as suddenly falling backward with flexion of the left limbs, erythrophoria of both eyes, and foaming at the mouth; the episode persisted for about one minute. The patient was admitted on August 20, 2007. Physical examination was unremarkable. Video-EEG monitoring revealed abnormal discharges in the bilateral occipital regions, with episodes originating from different areas of the bilateral occipital lobe (Figure 2A). MRI demonstrated abnormal signals in the bilateral occipital lobe (Figure 2B and C), and T2-T2 imaging showed irregular high signals in the bilateral occipital lobe that were suggestive of ischemic changes (Figure 2D). After a thorough preoperative evaluation, it was decided that bilateral occipital lobe surgery should be performed as the treatment strategy. After adequate preoperative preparation, a bilateral occipital craniotomy was performed under general anesthesia, and a subdural grid electrode was placed (Figure 2E and F). The intracranial electrode detected abnormal discharges that originated in both the left and right sides of the occipital lobe (Figure 2G-I). Bilateral resection was performed after the determination of the origins of the seizures and localization of cortical function. Postoperative cranial CT demonstrated the changes following bilateral occipital lobe surgery (Figure 2). The patient recovered well after surgery with good limb function and no defects in vision or the visual fields. The patient has not experienced any seizures during the 12 years since surgery was performed.

Case 2: An 11-year-old male patient (an elder twin) presented with a history of convulsions that began three d after birth. He was diagnosed as having a subarachnoid hemorrhage secondary to dystocia and was hospitalized for 11 d at XXX Hospital to receive treatment. At the age of 5 years, the patient began to experience transient facial convulsions characterized by small movements such as winking. The episodes occurred once every mo for several mos and were not associated with falling to the ground or loss of consciousness. A diagnosis of epilepsy was made on the basis of EEG investigations. By 9 years of age, the patient was experiencing seizures that were more frequent (typical interval of 5-7 d, with a maximum of 7 episodes in one day) and severe (all grand mal seizures). Treatment with oral Depakine (valproate sodium) was ineffective, so the medication was changed to Topamax (topiramate, 100 mg/d). However, the symptoms had worsened further by the time the patient was 10 years old, with typical convulsive episodes lasting 1-2 minutes and involving turning of both eyes, upper limb flexion, clenching of both hands, and loss of consciousness but no vomiting or urinary/fecal incontinence. By this stage, the seizures were frequently occurring (4-5 times/d), and the patient was showing poorer physical and intellectual development than his peers. There were no hereditary or similar diseases in the family, and the patient’s brother developed normally. At presentation, physical examination indicated that the patient had a short stature for his age (113 cm), but otherwise, the findings were unremarkable. Scalp video-EEG detected a total of 4 episodes in 24 h, with two originating in the left occipital lobe and two originating in the right occipital lobe (Figure 3A and B). MRI showed bilateral occipital dysplasia and a high signal on T2-FLAIR imaging that was obvious on the right side (Figure 3C-E). After bilateral occipital craniotomy and subdural grid electrode placement (Figure 3F), the EEG recording detected a total of 4 episodes in 24 h, with two episodes originating on each side. This confirmed the diagnosis of bilateral occipital lobe epilepsy. After surgical resection of the identified lesions, cranial CT was performed (Figure 3I). The patient was completely blind immediately after surgery, but visual function showed partial recovery by the time of discharge and was fully restored at 1 mo. The patient recovered well after surgery with good limb function and no complications. No seizures have occurred during the 12 years since surgery.

DISCUSSION

The main finding of this case series of patients treated surgically for bilateral occipital lobe epilepsy is that bilateral resection during a single operation was a very effective
Figure 2: Clinical findings in a 15-year-old male patient with bilateral occipital lobe epilepsy. A: Scalp video-electroencephalography (EEG) recordings demonstrated abnormal discharges in the right occipital region during the interictal period; B and C: magnetic resonance imaging (MRI) revealed abnormal...
signals in the bilateral occipital lobe; D: T2-FLAIR MRI showed irregular high signals in the bilateral occipital lobe that suggested ischemic changes; E: A subdural grid electrode was placed during surgery under general anesthesia; F: Anteroposterior and lateral head X-rays (taken after closure of the craniotomy) showing the position of the subdural grid electrode; G-I: Representative EEG recordings made using the subdural grid electrode showing abnormal discharges arising from both sides of the occipital lobe; The upper half of each trace shows recordings obtained from the left occipital lobe, and the lower half of each trace shows recordings obtained from the right occipital lobe; J: Postoperative cranial computed tomography.

Figure 3 Clinical findings in an 11-year-old male patient with bilateral occipital lobe epilepsy. A: Representative scalp video-electroencephalography (EEG) recording demonstrating abnormal discharges originating in the left occipital region during the interictal period; B: Representative scalp video-EEG recording demonstrating abnormal discharges originating in the right occipital region during the interictal period; C-E: Magnetic resonance imaging showing bilateral occipital dysplasia and a high signal on T2-FLAIR imaging that was obvious on the right side; F: Anteroposterior X-ray illustrating the position of the subdural grid electrode; G and H: Representative EEG recordings made using the subdural grid electrode showing abnormal discharges arising from both the left (G) and right (H) sides of the occipital lobe; I: Postoperative cranial computed tomography.

treatment, with most patients (85%) free of disabling seizures at 5 years after neurosurgery and no patients exhibiting no worthwhile improvement. Furthermore, most patients (65%) showed no visual field changes after surgery, although 15% developed a new visual field defect, and 20% exhibited worsening of a preexisting defect. Taken together, our results indicate that the resection of bilateral occipital lobe lesions during a single operation is an effective and safe treatment for bilateral occipital lobe epilepsy.

The clinical manifestations of bilateral occipital lobe epilepsy in our cohort of 20 patients were elementary visual hallucinations, flashing lights, blurred vision, visual field defects, blindness, visual illusions, blinking, a sensation of eye movement, dizziness, and deja vu. These manifestations are typical of the visual and oculomotor symptoms of occipital lobe epilepsy reported by others[1,7-9,15,19-30]. Although the pathology underlying occipital lobe epilepsy can vary, the pathologic diagnoses made in our patients have also been reported previously[7-9,19-29].

In the present study, 90% of the patients were classified as seizure-free (Engel grade I) postoperatively and at the 1-year follow-up, while 85% were considered seizure-free.
at 3 years and ≥ 5 years. In previous clinical research, the proportions of patients with occipital lobe epilepsy achieving a postoperative seizure-free status were reported to be 100%[27], 71%[7], 69%[25], 67%[28], 64%[8], 63%[24], 62%[9], 60%[29], 58%[21], 55%[26], 50%[19,25], and 46%[20,22]. Thus, the effectiveness of our surgical technique was at least comparable to that described in the above studies and in a recent meta-analysis[16]. This would imply that resecting epileptic foci from both sides of the occipital lobe during a single operation does not compromise the clinical effectiveness of surgery.

Lesions to the occipital lobe, which plays a central role in visual function, can result in visual field defects[32]. Thus, occipital lobe surgery for epilepsy is associated with a substantial risk of aggravating existing visual field defects or creating new ones[26]. In previous clinical research, surgical treatment of occipital lobe epilepsy was reported to induce new visual field defects or worsen preexisting visual field defects in 81%[9], 76%[7], 62%[8], 57%[25], 50%[28], 42%[23], and 30%[24] of cases. In the present study, only 15% of patients developed a new visual field defect, and only 20% exhibited aggravation of a preexisting defect. Notably, two of the patients in the present study exhibited substantial improvements in visual function after surgery (as described in the Results section), suggesting that the removal of lesions improved the functioning of remaining healthy brain tissue. Thus, the safety of our technique regarding the preservation of the visual fields appears to be, at the very least, comparable to that described in earlier studies, and some patients may show better visual function after one-stage surgery.

Two interesting additional observations in this study were a reduction in the number and sizes of facial sebaceous adenoma lesions in one patient and the resolution of drug-resistant psoriatic lesions in another patient after surgery. The reasons for these unexpected findings are not known. However, psychological distress is prevalent in people with epilepsy[33], and stress is acknowledged as an aggravating factor for psoriasis[34,35]. Thus, it is possible that the successful surgical treatment of drug-resistant epilepsy had other beneficial effects mediated via reduced levels of psychologic stress.

This study has some limitations. First, this was a retrospective analysis and hence was potentially prone to selection bias and information bias. Second, this was a two-center study with a small sample size, so the generalizability of our findings is not known. Third, we did not include a comparator group in which a two-stage (conventional) surgical resection was carried out. A prospective, randomized clinical trial with a comparator group is needed to confirm our results.

CONCLUSION

In conclusion, the resection of bilateral occipital lobe lesions during a single operation is an effective and safe treatment for bilateral occipital lobe epilepsy. The use of this approach would provide several benefits over conventional two-stage treatment, including a shorter treatment cycle, fewer operations/hospitalizations, and lower cost.

ARTICLE HIGHLIGHTS

Research background

Neurosurgical treatment of severe bilateral occipital lobe epilepsy usually involves two operations several mos apart.

Research motivation

The surgical treatment of bilateral occipital lobe epilepsy during a single operation would have several potential advantages, such as a reduced number of surgeries and hospitalizations, a shorter treatment time, lower treatment costs, and decreased psychological stress for the patients and their families.

Research objectives

To evaluate surgical resection of bilateral occipital lobe lesions during a single operation as a treatment for bilateral occipital lobe epilepsy.

Research methods

This retrospective case series included patients with drug-refractory bilateral occipital
lobe epilepsy treated surgically between March 2006 and November 2015.

Research results
Most patients were free of disabling seizures (Engel grade I) postoperatively (18/20, 90.0%) and at 1 year (18/20, 90.0%), 3 years (17/20, 85.0%) and ≥ 5 years (17/20, 85.0%). No patients were classified Engel grade IV (no worthwhile improvement). After surgery, there was no change in visual function in 13/20 (65.0%), development of a new visual field defect in 3/20 (15.0%), and worsening of a preexisting defect in 4/20 (20.0%).

Research conclusions
Resection of bilateral occipital lobe lesions during a single operation may be applicable in bilateral occipital lobe epilepsy.

Research perspectives
A prospective, randomized clinical trial with a comparator group is needed to confirm our results.

ACKNOWLEDGEMENTS
The authors thank all the patients and their families for their agreement to participate in this study.

REFERENCES

Retrospective Study

Improving rehabilitation and quality of life after percutaneous transhepatic cholangiography drainage with a rapid rehabilitation model

Lu-Lu Xia, Ting Su, Yan Li, Jun-Fang Mao, Qi-Hong Zhang, Yang-Yan Liu

Abstract

BACKGROUND
Percutaneous transhepatic cholangiography drainage (PTCD) effectively treats biliary obstruction. However, patients must maintain the drainage tube after hospital discharge, which may interfere with daily life and work, potentially causing psychological distress. Postoperative rehabilitation is crucial, and strengthened nursing interventions can shorten recovery time.

AIM
The aim was to evaluate an inpatient model to shorten rehabilitation duration and improve quality of life after PTCD.

METHODS
A total of 118 patients with malignant obstructive jaundice who were admitted to our hospital between May 2018 and January 2021 were included and divided into observational (with therapy) and control (no therapy) groups of 59 each.

RESULTS
The observational group had fewer hospitalization days than the control group. The complication, the PTCD fixed-tube prolapse, and tube-related admission rates...
within 3 mo after PTCD were significantly lower in the observation group than in the control group ($P < 0.05$). The fatigue, pain, nausea, vomiting, pruritus, emaciation, and fever scores after PTCD decreased in both groups compared with the scores before PTCD ($P < 0.05$). The quality of life scores after the intervention were higher in the observation than in the control group ($P < 0.05$).

**CONCLUSION**
The model promoted rehabilitation after PTCD, reduced post-PTCD complications, and the tube-related admissions in the 3 mo after the procedure, and improved the quality of life.

**Key Words:** Rapid rehabilitation model; Percutaneous transhepatic cholangiography drainage; Quality of life; Complications

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** This retrospective study found that a rapid recovery model promoted the recovery of patients after percutaneous transhepatic cholangiography drainage intervention, reduced intervention-related complications and catheter-related admissions within 3 mo of intervention, and improved quality of life.

**INTRODUCTION**
Malignant obstructive jaundice is a form of biliary obstructive jaundice caused by malignant tumors[1,2]. Patients often have potentially fatal, severe complications, such as malnutrition and immune dysfunction[3]. Further, patients are often in an advanced disease stage, commonly secondary to infections and liver failure, making surgery more difficult. Therefore, patients with malignant obstructive jaundice require timely and effective treatment to protect liver function, improve immune function, and enhance resistance. Percutaneous transhepatic biliary drainage (PTCD) is a safe and effective method for palliative malignant obstructive jaundice treatment[4]. PTCD reduces the severity of jaundice, alleviates biliary obstruction, improves the quality of life, and prolongs patient survival[5]. After PTCD treatment, patients must maintain the drainage tube outside of the hospital for a sustained period, which may cause significant disruption of their daily life and work, potentially causing psychological disorders.

Postoperative rehabilitation is important for patients with trauma and strengthening nursing measures can improve the speed of recovery[6]. Thus, the comprehensive treatment and nursing protocols implemented in the rapid rehabilitation nursing model have been well-received by most patients. The model reduces rehabilitation time, the complication rate, and patient pain and psychological distress[7,8]. This study retrospectively assessed the rapid rehabilitation model after PTCD for patients with malignant obstructive jaundice to determine any rehabilitation or quality of life improvements and provide a reference clinical treatment.

**MATERIALS AND METHODS**

**Patients**
Patients with malignant obstructive jaundice treated with PTCD at our hospital between May 2018 and January 2021 were retrospectively analyzed. The inclusion criteria were (1) meeting the criteria for malignant obstructive jaundice[9,10] (i.e.
distinct symptoms and signs related to obstructive jaundice, such as jaundice, abdominal pain, and fever, or symptoms accompanied by abdominal distension, fatigue, and anorexia; significantly increased indicators of liver dysfunction or abnormal tumor markers; a B-ultrasound-, computed tomography- and magnetic resonance cholangiopancreatography-confirmed malignant lesion, and pathologically confirmed biliary obstruction caused by the malignant tumor; (2) ≥ 18 years and ≤ 75 years of age; (3) having tumors above tumor node metastasis stage T3 with no possibility of surgical treatment; (4) treatment with PTCD; and (5) availability of complete clinical data. Patients with (1) cardiopulmonary dysfunction; (2) jaundice caused by other factors; (3) a Canovschi overall health score of < 70; (4) mental illness or psychological disease; and (5) a history of biliary tract surgery or radical surgery were excluded. The patients were divided into routine intervention (the control group) and rapid rehabilitation intervention (the observation group).

**Surgical methods**
The location of the obstruction was identified by preoperative imaging. Intercostal spaces 8-10 in the right axillary midline were selected as a puncture point for patients with common bile duct and right hepatic duct obstruction. The puncture point was under the xiphoid process for patients with left hepatic duct obstruction. Routine disinfection and draping were performed with the patient in the supine position, and local anesthesia was administered using 2% lidocaine. The needle was inserted layer by layer using X-ray fluoroscopy to avoid large blood vessels as much as possible. After the puncture needle entered the dilated bile duct, the needle core was removed and bile was withdrawn. Iohexol was injected for comparative imaging to identify the internal and external bile ducts and liver obstruction sites. A guidewire was inserted, and a decision regarding balloon dilatation was made based on the occlusion. A drainage tube or biliary stent was placed along the guidewire. After confirming that the drainage tube and stent were in a good position and barrier-free, they were reimaged, and the drainage tube was externally fixed and connected to a drainage bag.

**Therapeutic methods**
The control group received routine intervention with preoperative preparation and intraoperative monitoring. The patients also received standard postoperative education and were provided with discharge guidance. The observation group received the rapid rehabilitation model intervention, comprising preoperative health education, psychological care, and preoperative preparation guidelines. Health education included informing patients about the disease, treatment plan, and postoperative prevention measures. Psychological care provided counseling based on the patient’s condition and was intended to improve their mood and treatment compliance. Regarding preoperative preparation, the dietary requirements were explained, and supervision was initiated to ensure fasting and hydration status at prescribed times. However, situational consideration for each patient meant that some were allowed an appropriate amount of glucose saline. Intraoperative care required patients to actively cooperate with the attending doctor and consult with the nursing staff. Appropriate intraoperative methods reduced patient tension and anxiety, allowing for better cooperation. Postoperative basic care, activity, and dietary care were also performed. Basic postoperative nursing care included routine fluid replacement, monitoring vital signs, lying on the back for 6 h, based on clinical symptoms, biochemical indicators, and postoperative cholangiography, and monitoring the blood, liver function, and electrolytes 1 to 3 d after the operation. Patients were advised about analgesia, pain score, and avoiding infection and complications related to use of the analgesic pump installed during the operation. Personalized rehabilitation plans were created situationally based on patient limb and joint movements, dietary requirements, and formulated with attention to the appropriate limb-joint movement times. For example, some patients could drink water appropriately 4 h after surgery and eat food about 12 h later to promote intestinal function recovery. After discharge, the caregiver informed the patient of precautions and requirements.

**Patient data**
The length of hospital stay and complications, including hemorrhage, pancreatitis, biliary infection, and stent occlusion, were recorded for all patients. The emergence of PTCD tube fixation was classified as no emergence, partial emergence (catheter shift ≤ 1 cm), and complete emergence (catheter shift > 1 cm). Catheter prolapse included partial and complete prolapse. A hospital-made questionnaire was used to assign a
PTCD catheter mastery score to assess patient knowledge of PTCD, including catheter care, observation, and prevention of complications, observation of drainage fluid, and observation and care of wounds. Scores ranged from 0 to 10 points for a single aspect, with 0 points indicating non-mastery and 10 points indicating proficiency. Malignant obstructive jaundice-specific quality of life was assessed using a scoring system that included fatigue, pain, nausea and vomiting, itching, weight loss, and fever. The higher the score, the lower the quality of life.

**Test method**
Fasting venous blood (3–5 mL) was collected from the antecubital area in the morning and centrifuged at 3000 r/min for about 10 min to obtain the serum. A quantitative analyzer (QR-1000; Shenzhen Huisong Technology Development Co., Ltd., Shenzhen, China) to assay C-reactive protein (CRP, normal range, 0 to 10 mg/L). An automated hematology analyzer (LH750, Beckman Coulter, Brea, CA, USA) was used to determine leukocyte counts (normal range, 4.0 × 10^9/L to 10.0 × 10^9/L). A Cobas C310 automated biochemical analyzer (Roche, Switzerland) was used to test liver function indicators [e.g., total bilirubin (TBIL), alkaline phosphatase (ALP), total bile acids (TBAs), and alanine aminotransferase (ALT)] before and after treatment.

**Statistical analysis**
SPSS version 19.0 (IBM Corp., Armonk, NY, United States) was used for the statistical analysis. Results were reported as means ± SD. Independent sample t-tests were used for intergroup comparisons, and paired t-tests were used for intragroup comparisons. \( \chi^2 \) tests was used for rate comparisons. \( P \) values of < 0.05 indicated statistical significance.

**RESULTS**

**Demographic information**
In total, 118 patients with malignant obstructive jaundice were treated with PTCD in our hospital between May 2018 and January 2021; 66 were men, and 52 were women, and their average age was 63.85 ± 8.05 years. The routine intervention and rapid rehabilitation intervention groups each included 59 patients. General demographic data, sex, location of the obstruction, disease type, and educational background, did not differ between the groups (\( P > 0.05; \) Table 1).

**Hospital stay and the pipeline-related hospitalization within 3 mo after PTCD**
The observation group had fewer hospitalization days than the control group. In addition, the pipeline-related admission rate within 3 mo after PTCD was significantly lower in the observation group than in the control group (\( P < 0.05; \) Table 2).

**ALP, ALT, TBIL, and TBA**
ALP, ALT, TBIL, and TBA did not differ between the groups before PTCD (\( P > 0.05 \)). In both groups, all four significantly decreased after PTCD compared with before PTCD (\( P < 0.05 \)). After PTCD, all factors were significantly lower in the observation group than in the control group (\( P < 0.05; \) Table 3).

**White blood cell count and CRP level**
White blood cell (WBC) count and CRP level did not differ between the groups before PTCD (\( P > 0.05 \)) but they significantly had decreased in both groups after PTCD (\( P < 0.05 \)). After PTCD, both factors were lower in the observation group than in the control group (\( P < 0.05; \) Table 4).

**PTCD fixed-tube prolapse and complication rates**
The PTCD fixed-tube prolapse rate and the complication rate were both significantly lower in the observation group than in the control group (\( P < 0.05; \) Tables 5 and 6).

**PTCD band-catheter mastery scores**
Before PTCD, the PTCD cannulation mastery scores (i.e. PTCD proficiency) did not differ between the groups (\( P > 0.05 \)). However, the scores for PTCD cannulation nursing care, observing and preventing complications, observing drainage liquid, and observing and caring for wounds significantly increased compared with the scores before PTCD in both groups (\( P < 0.05 \)). The scores were higher in the observation
### Table 1 Demographic characteristics, n (%)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group (n = 59)</th>
<th>Observation group (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (57.63)</td>
<td>32 (54.24)</td>
</tr>
<tr>
<td>Female</td>
<td>25 (42.37)</td>
<td>27 (45.76)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62.95 ± 9.02</td>
<td>62.01 ± 9.75</td>
</tr>
<tr>
<td>Obstruction site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>37 (62.71)</td>
<td>31 (52.54)</td>
</tr>
<tr>
<td>High position</td>
<td>22 (37.29)</td>
<td>28 (47.46)</td>
</tr>
<tr>
<td>Disease type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hilar cholangiocarcinoma</td>
<td>33 (55.93)</td>
<td>30 (50.08)</td>
</tr>
<tr>
<td>Middle-lower cholangiocarcinoma</td>
<td>14 (23.73)</td>
<td>15 (25.42)</td>
</tr>
<tr>
<td>Pancreatic Head Cancer</td>
<td>4 (6.78)</td>
<td>8 (13.56)</td>
</tr>
<tr>
<td>Ampullary carcinoma</td>
<td>8 (13.56)</td>
<td>6 (16.95)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junior high school and below</td>
<td>8 (13.56)</td>
<td>10 (16.95)</td>
</tr>
<tr>
<td>Technical secondary school and high school</td>
<td>19 (32.30)</td>
<td>17 (28.81)</td>
</tr>
<tr>
<td>College degree and above</td>
<td>32 (54.24)</td>
<td>32 (54.24)</td>
</tr>
<tr>
<td>Medical insurance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical insurance</td>
<td>31 (52.54)</td>
<td>27 (45.76)</td>
</tr>
<tr>
<td>Business insurance</td>
<td>16 (27.12)</td>
<td>17 (28.81)</td>
</tr>
<tr>
<td>Own expense</td>
<td>12 (20.34)</td>
<td>15 (25.42)</td>
</tr>
</tbody>
</table>

### Table 2 Hospitalization after percutaneous transhepatic cholangiography drainage

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of days</th>
<th>Pipeline-related admissions$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>15.23 ± 3.02</td>
<td>8 (13.56)</td>
</tr>
<tr>
<td>Observation</td>
<td>13.12 ± 2.15$^a$</td>
<td>1 (1.69)$^a$</td>
</tr>
</tbody>
</table>

$^aP < 0.05$ vs control group.
$^bP < 0.05$ vs control 3 mo after surgery.

Data are n (%) or mean ± SD.

After PTCD, the quality of life scores did not differ between the groups ($P > 0.05$). After PTCD, fatigue, pain, nausea, vomiting, pruritus, emaciation, and fever scores had decreased in both groups ($P < 0.05$). The quality of life scores were significantly higher after PTCD in the observation group than in the control group ($P < 0.05$; Table 8).

### DISCUSSION

The PTCD procedure is minimally traumatic, relatively convenient, widely applicable, and especially suitable for patients in poor condition, patients who cannot tolerate general anesthesia, and patients with a history of previous gastrointestinal surgery and deformities. However, PTCD has disadvantages. The tube is used for a long time and requires maintenance after hospital discharge. Therefore, patients may suffer from...
Table 3 Alkaline phosphatase, alanine aminotransferase, total bilirubin, and total bile acid before and after percutaneous transhepatic cholangiography drainage (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>ALP (U/L)</th>
<th>ALT (U/L)</th>
<th>TBIL (μmol/L)</th>
<th>TBA (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Control</td>
<td>405.63 ± 53.69</td>
<td>195.89 ± 23.16</td>
<td>121.36 ± 29.12</td>
<td>49.23 ± 6.02</td>
</tr>
<tr>
<td>Observation</td>
<td>412.05 ± 48.76</td>
<td>184.25 ± 18.44</td>
<td>123.63 ± 25.78</td>
<td>42.02 ± 5.69</td>
</tr>
</tbody>
</table>

aP < 0.05 vs pre-intervention.
bP < 0.05 vs control group.

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; TBA: Total bile acid; TBIL: Total bilirubin.

Table 4 White blood cell count and C-reactive protein before and after percutaneous transhepatic cholangiography drainage (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>WBC (× 10^9/L)</th>
<th>CRP (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Control</td>
<td>14.69 ± 2.15</td>
<td>8.45 ± 1.03</td>
</tr>
<tr>
<td>Observation</td>
<td>14.71 ± 2.32</td>
<td>7.91 ± 0.89</td>
</tr>
</tbody>
</table>

aP < 0.05 vs before percutaneous transhepatic cholangiography drainage.
bP < 0.05 vs control group.

CRP: C-reactive protein; WBC: White blood cells.

Table 5 Percutaneous transhepatic cholangiography drainage prolapse, n (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>None</th>
<th>Partial</th>
<th>Complete</th>
<th>Escape rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>48 (81.36)</td>
<td>8 (13.56)</td>
<td>3 (5.08)</td>
<td>11 (18.64)</td>
</tr>
<tr>
<td>Observation</td>
<td>57 (96.61)</td>
<td>2 (3.39)</td>
<td>0 (0.00)</td>
<td>2 (3.39)</td>
</tr>
</tbody>
</table>

aP < 0.05 vs control group.

Table 6 Complications after percutaneous transhepatic cholangiography drainage, n (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Bleeding</th>
<th>Pancreatitis</th>
<th>Biliary tract</th>
<th>Blocked stent infection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3 (5.08)</td>
<td>1 (1.69)</td>
<td>4 (6.78)</td>
<td>2 (3.39)</td>
<td>10 (16.95)</td>
</tr>
<tr>
<td>Observation</td>
<td>1 (1.69)</td>
<td>0 (0.00)</td>
<td>2 (3.39)</td>
<td>0 (0.00)</td>
<td>3 (5.08)</td>
</tr>
</tbody>
</table>

aP < 0.05 vs control group.

There were significantly fewer hospitalization days and a lower tube-related admission rate within 3 mo after PTCD in the observation group than in the control group. The rapid rehabilitation nursing model also improved the understanding and mastery of PTCD catheter-related knowledge, reducing complications, and the postoperative complications, such as hemophilia, bile leakage, bacterial retrograde infection, and stent blockage[11-13]. A targeted nursing intervention model is thus necessary to ensure a successful operation and proper tube use. The rapid rehabilitation nursing model was implemented at our hospital for postoperative care of patients and to provide health guidance so that patients have a better understanding of the nursing and rehabilitation processes. Further, psychological and dietary care can aid patient recovery. At the same time, regular ward rounds by nursing staff can improve the understanding of each patient’s status, allowing for shortcomings in nursing care to be identified and improved upon, aiding comprehensive and rapid rehabilitation, and reducing recovery time[14,15].
Xia LL et al. Improving rehabilitation with a rapid rehabilitation model

Table 7 Tube-related knowledge mastery scores before and after percutaneous transhepatic cholangiography drainage (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>PTCD tube care Before</th>
<th>PTCD tube care After</th>
<th>Complications Before</th>
<th>Complications After</th>
<th>Drainage fluid Before</th>
<th>Drainage fluid After</th>
<th>Wound care Before</th>
<th>Wound care After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.15 ± 0.54</td>
<td>7.23 ± 0.46&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.85 ± 0.39</td>
<td>7.14 ± 0.55&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.03 ± 0.41</td>
<td>7.25 ± 0.45&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.63 ± 0.41</td>
<td>7.74 ± 0.46&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Observation</td>
<td>5.06 ± 0.61</td>
<td>8.72 ± 0.51&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.82 ± 0.45</td>
<td>8.83 ± 0.57&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.10 ± 0.38</td>
<td>8.57 ± 0.43&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.58 ± 0.46</td>
<td>9.14 ± 0.41&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05 vs before percutaneous transhepatic cholangiography drainage.
<sup>b</sup>P < 0.05 vs control group.
PTCD: Percutaneous transhepatic cholangiography drainage.

Table 8 Quality of life scores before and after percutaneous transhepatic cholangiography drainage (mean ± SD, min)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group Before</th>
<th>Control group After</th>
<th>Observation group Before</th>
<th>Observation group After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>78.23 ± 8.69</td>
<td>32.63 ± 5.36</td>
<td>77.96 ± 10.03</td>
<td>23.05 ± 4.96</td>
</tr>
<tr>
<td>Pain</td>
<td>66.23 ± 9.65</td>
<td>35.26 ± 4.85</td>
<td>65.96 ± 10.02</td>
<td>19.36 ± 5.02</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>68.77 ± 10.45</td>
<td>30.36 ± 4.12</td>
<td>69.02 ± 9.52</td>
<td>18.26 ± 3.69</td>
</tr>
<tr>
<td>Itching</td>
<td>65.32 ± 9.21</td>
<td>22.05 ± 8.14</td>
<td>64.53 ± 10.23</td>
<td>14.26 ± 4.12</td>
</tr>
<tr>
<td>Emaciation</td>
<td>62.55 ± 4.85</td>
<td>41.05 ± 3.86</td>
<td>62.85 ± 5.17</td>
<td>32.63 ± 4.02</td>
</tr>
<tr>
<td>Fever</td>
<td>58.69 ± 8.96</td>
<td>27.41 ± 6.11</td>
<td>59.04 ± 9.41</td>
<td>22.03 ± 4.01</td>
</tr>
</tbody>
</table>

CRP is an acute-phase reaction protein. When the body is attacked by viruses, pathogenic bacteria, or other substances, the serum CRP content significantly increases. For example, a significant increase in CRP levels can be detected within hours after the onset of a bacterial blood infection<sup>[16]</sup>. A WBC count is a primary component of a routine blood examination and also an important indicator of acute infectious diseases. When acute severe inflammation, acute suppurative inflammation, bacterial infection, and severe tissue damage occur, WBC changes are significant<sup>[17, 18]</sup>. In this study, the WBC count and CRP levels significantly decreased in both groups after PTCD compared with before PTCD, and were lower in the observation group than in the control group after PTCD. The results indicate that postoperative infection can be reduced by reasonable nursing methods. ALP, ALT, TBIL, and TBA also decreased in both groups after PTCD compared with before PTCD, and were lower in the observation group than in the control group after PTCD. The results suggest that both postoperative nursing interventions effectively reduced yellowing and liver damage, but the rapid rehabilitation nursing model was more effective in improving liver function. Evaluation of the perioperative nursing process demonstrated that the nursing staff closely observed the patient's vital signs, provided timely treatment in abnormal situations, ensured smooth progress of the operation, and improved the overall quality and effectiveness of care. As such, patients with a high degree of cooperation and quality of care had a reduced occurrence of postoperative infections.
The prolapse and PTCD fixation-tube complication rates in the observation group were significantly lower than in the control group. Catheter removal and occlusion were the most common complications in patients after PTCD despite both groups receiving discharge guidance. However, appropriate guidance was not provided to patients in the control group, and was subsequently forgotten. Patients in the observation group maintained a long-term grasp of the relevant knowledge, and when patients had doubts regarding catheter placement, they were resolved through out-of-hospital follow-up, greatly reducing the incidence of complications. In the rapid rehabilitation model, the nursing staff strengthened the disease-related guidance to facilitate patients’ long-term memory and improve their understanding of the information. The mastery scores of PTCD tube care, observing and preventing complications, observing drainage fluid, and observing and caring for wounds increased in both groups after compared with before PTCD. However, the quality of life scores for fatigue, pain, nausea, vomiting, pruritus, emaciation, and fever decreased in both groups. The mastery scores for PTCD tube knowledge after PTCD were higher in the observation group than in the control group, as were the quality of life scores, indicating that the nursing staff comforted and fully informed the patients. Further, they thoroughly understood the patients’ emotions, consequently reducing negative feelings that helped to improve PTCD treatment preparation.

Postoperatively, nurses should closely observe patients’ vital signs and the drainage fluid properties, fix the drainage tube, maintain effective drainage, and give extra care to catheter removal, while also improving their awareness and care for complications, such as bile leakage and hemorrhage. In nursing, the patients are holistically treated, with emphasis on patient-centered and personalized care, while ensuring the continuity and quality of overall care, thereby improving patient quality of life after surgery[19,20].

Presently, there are many nursing interventions for patients after PTCD procedures, and a unified nursing method has not been adopted. This innovative study applied the rapid recovery model to perioperative patient care after PTCD to improve therapeutic efficacy and safety and reduce complications. However, the study was limited by the small sample size. Further studies with more participants could further support the conclusions.

CONCLUSION
The rapid rehabilitation model promoted the rehabilitation of patients after PTCD, reduced postoperative complications, reduced tube-related admission rate within 3 mo after PTCD, and improved patient quality of life.

ARTICLE HIGHLIGHTS
Research background
Percutaneous transhepatic cholangiography and drainage (PTCD) is an effective way to treat biliary obstruction. However, patients need to keep the drainage tube after they are discharged from the hospital. Enhanced nursing measures can increase the speed of recovery.

Research motivation
The motivation was to improve the recovery of patients after percutaneous transhepatic cholangiography drainage.

Research objectives
The study aimed to evaluate a rapid inpatient rehabilitation model to improve care, rehabilitation time, and patient quality of life after PTCD.

Research methods
A group study was conducted in 118 patients with malignant obstructive jaundice admitted to our hospital between May 2018 and January 2021.

Research results
The length of stay was shorter and the overall recovery level was better in the
observation group than that of the control group.

**Research conclusions**

The rapid rehabilitation model promoted rehabilitation after PTCD, reduced post-PTCD complications, and reduced the tube-related admission rate within 3 mo after PTCD, and improved patient quality of life.

**Research perspectives**

The rapid recovery model improved recovery after PTCD, improved the patient quality of life, and potentially has broad clinical application.

**REFERENCES**


Retrospective Study

Combined lumbar muscle block and perioperative comprehensive patient-controlled intravenous analgesia with butorphanol in gynecological endoscopic surgery

Rong-Yu Zhu, Si-Qu Xiang, Dou-Ren Chen

Abstract

**BACKGROUND**
Laparoscopic surgery has become a common surgical approach for the clinical treatment of intra-abdominal lesions in recent years. We hypothesized that lumbar block with postoperative patient-controlled intravenous analgesia (PCIA) by butorphanol after gynecological surgery under general anesthesia would be more effective than PCIA by butorphanol alone.

**AIM**
To investigate the effect of lumbar block with PCIA by butorphanol after gynecological surgery under general anesthesia.

**METHODS**
This study assessed 120 women scheduled for laparoscopic surgery at our hospital between May 2017 and May 2020. They were divided using a random number table into a research group (those who received quadratus lumborum block combined with PCIA analgesia by butorphanol) and a control group (those who received only PCIA analgesia by butorphanol), with 60 patients in each group. Demographic factors, visual analog scale scores for pain, serum inflammatory markers, PCIA compressions, Ramsay scores, and adverse events were compared between groups using a t-test, analysis of variance, or χ² test, as appropriate.

**RESULTS**
There were no significant differences in demographic factors between groups (all \( P > 0.05 \)). The visual analog scale scores of the research group in the resting state were significantly lower than those of the control group.
12 h and 24 h postoperatively were significantly lower than those of the control group \( (P < 0.05) \). Two hours after surgery, there were no significant differences in the levels of serum tumor necrosis factor-\( \alpha \), interleukin (IL)-6, or IL-8 between groups \( (P > 0.05) \). The serum tumor necrosis factor-\( \alpha \) levels of the research group 24 h postoperatively were significantly lower than those of the control group \( (P < 0.05) \). The levels of serum IL-6 and IL-8 in the study group 24 h and 48 h postoperatively were significantly lower than those in the control group \( (P < 0.05) \).

**CONCLUSION**

Lumbar block with PCIA with butorphanol after gynecological surgery under general anesthesia significantly improves the analgesic effect and reduces the degree of inflammation, instances of PCA compression, and adverse reactions.

**Key Words:** Quadratus lumborum block; Butorphanol; Patient-controlled intravenous analgesia; Analgesic effect

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

---

**Core Tip:** A total of 120 cases of patients undergoing laparoscopic surgery in our hospital were taken as the research subjects, and it was confirmed that gynecological surgery combined with patient-controlled intravenous analgesia combined with butorphanol can significantly improve the analgesic effect, reduce the degree of inflammation, reduce the times of patient-controlled intravenous analgesia compression, and adverse reactions in patients.

---

**INTRODUCTION**

After the establishment of \( \mathrm{CO}_2 \) pneumoperitoneum during gynecological laparoscopic surgery, the focal tissues need to be completely removed, resulting in surgical trauma. General anesthesia guarantees adequate analgesia and sedation during laparoscopic surgery and maintains hemodynamic stability during the operation[1,2]. However, if postoperative pain is not effectively controlled, the neuroendocrine-immune network is activated, the risk of postoperative complications is increased, and patients can experience negative emotions and sleep disorders, which are not conducive to physical or mental health[3]. Inhibiting the immune function of patients with gynecological malignancies can also lead to tumor escape, increasing the risk of tumor recurrence or metastasis after surgery[4-8]. Therefore, active analgesic therapy is needed after gynecological laparoscopic surgery[9,10].

Patient-controlled intravenous analgesia (PCA) is a common and convenient analgesic method after general anesthesia. Patients control the release of analgesic drugs by pressing an analgesic pump as required to obtain pain relief. However, the excessive use of anesthetics can cause a variety of adverse reactions[11]. Therefore, some scholars have suggested that early postoperative multimodal analgesia can be used to accelerate rehabilitation, and regional block is an important aspect of multimodal analgesia that can reduce surgical stress and the required dose of anesthetics[12,13]. Here, the results of a study exploring the effects of lumbar block combined with PCA with butorphanol on postoperative analgesia after gynecological surgery under general anesthesia are reported[11,13].
MATERIALS AND METHODS

General information
We selected 120 women scheduled for laparoscopic surgery in our hospital between May 2017 and May 2020 and randomly divided them into two equal groups (both \( n = 60 \)) depending on if they received lumbar block with PCIA by butorphanol (research group) or PCIA by butorphanol alone (control group). The inclusion criteria were as follows: (1) Patients who underwent gynecological laparoscopic surgery; (2) Age 37-years-old to 75-years-old; (3) No missing information; and (4) The patients or their families gave informed consent before the implementation of this study, which was approved by the medical ethics committee. The exclusion criteria were as follows: (1) Unconfirmed pathological diagnosis; (2) Acute myocardial infarction, mental illness, or chronic renal dysfunction; (3) Alzheimer’s disease or language and communication disorders; (4) Other malignant tumors; or (5) Missing data.

Patients in the research group were 37-years-old to 75-years-old, with an average age of 57.7 ± 7.8 years. Patients in the control group were 40-years-old to 75-years-old, with an average age of 55.8 ± 7.1 years. There was no significant difference in age between the two groups (\( P > 0.05 \)).

Anesthesia and postoperative analgesia method
Both groups received laparoscopic surgery under general anesthesia, routine electrocardiogram monitoring after entering the room, and detection for bispectral index by sticking electrodes on the forehead. Anesthesia was induced by successive intravenous injection of 0.05 mg/kg midazolam, 3.0 mg/kg fentanyl, 1.5-2.0 mg/kg propofol, and 0.15 mg/kg cisatracurium. Endotracheal intubation was performed after the eyelash reflex disappeared and was connected to the anesthesia machine for mechanical ventilation, with a tidal volume of 6-8 mL/kg and respiratory rate of 8-12 breaths/min. Fentanyl (1 μg/kg) was injected intravenously before skin incision, with continuous maintenance by 4-6 mg/kg propofol and 0.1-0.2 μg/kg/min remifentanil. Cisatracurium was injected intermittently to maintain muscle relaxation with a bispectral index value of 45-55. When systolic blood pressure was higher than basal systolic blood pressure by 25%, nitroglycerin was used to control blood pressure. When systolic blood pressure was lower than basal systolic blood pressure by 25%, ephedrine or norepinephrine was adopted to boost blood pressure. Atropine was given when the heart rate was below 50 bpm, and esmolol was given when it was above 100 bpm. Propofol administration was stopped before skin suturing and remifentanil at the end of operation.

The control group was given PCIA analgesia by butorphanol at the end of the operation. The PCIA formula consisted of 0.125 mg/kg butorphanol, 8 mg tropisetron, and normal saline to 100 mL. The background infusion dose was 2 mL, a single dose was 3 mL, and the locking time was 15 min.

The research group was treated with quadratus lumborum block combined with the same PCIA analgesia protocol as the control group. Quadratus lumborum block was performed as follows. The patient was placed in the lateral position with local disinfection and a towel. The ultrasonic probe was placed horizontally on the anterior superior iliac spine near the axillary midline. An oval muscle was seen at the aponeurosis formed by the transverse abdominal muscle, referred to as the quadratus lumbalis. The classic “clover” structure was seen when the ultrasonic probe was tilted caudally. After performing puncture 0.5-1.0 cm behind the ultrasonic probe, 1-2 mL of 2% lidocaine was injected for local anesthesia. With the guidance of ultrasound, the needle was inserted from the dorsal side toward the ventral side to the posterolateral edge of the quadratus psoas muscle. If no gas or liquid was pumped back, 1-2 mL of normal saline was injected to confirm the position. After local injection of 20 mL 0.375% ropivacaine, local anesthetic drugs could be seen in the psoas quadratus muscle after the formation of an anechoic shadow under ultrasound. The contralateral side was blocked by the same method. If local anesthetic poisoning occurred during the injection, the injection was stopped immediately, and oxygen and sedation treatment were administered. Patients with convulsions were given an intravenous injection of propofol and succinylcholine. If circulatory failure occurred, immediate supportive treatment such as rapid fluid infusion, pressors, and cardiotropic and auxiliary ventilation was administered. Cardiopulmonary resuscitation was performed in the event of cardiac arrest.

Measurements
The measurements compared between the groups were as follows. The analgesic effect
was assessed by a 10-point visual analog scale (VAS) for pain[14]. The more severe the pain, the higher the VAS score. The number of PCIA compressions and the levels of inflammatory factors [serum tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8] were assessed at different timepoints. The Ramsay score[15] was used to assess patients’ levels of consciousness (1 point, the patient is restless and irritable; 2 points, the patient is quiet and cooperative; 3 points, the patient is sleepy and can follow instructions; 4 points, the patient is asleep but can be woken up; 5 points, the patient is asleep, sluggish, and only responds to strong stimulation; and 6 points, the patient is deeply asleep and hard to wake up). The incidence rates of postoperative anesthesia-related adverse reactions were also compared.

To measure serum inflammatory factors, 3 mL of peripheral venous blood were collected at 4, 12, 24, and 48 h after the operation and centrifuged at 3500 rpm for 10 min within 1 h of collection. TNF-α, IL-6, and IL-8 were detected by enzyme-linked immunosorbent assay (Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China) on a RT-96A microplate reader (Shenzhen Mindray Medical Electronics Co., Ltd., Shenzhen, China).

Statistical processing
SPSS 21.0 software (IBM, Armonk, NY) was used for data processing. All measurements were normally or approximately normally distributed and expressed as mean ± SD. The t-test was used to compare non-repeated data between groups. Repeated measurement data were analyzed by repeated-measures analysis of variance. The least significant difference t-test was used to compare timepoints. Count data were analyzed by the χ² test. Statistical significance was established at P = 0.05.

RESULTS

Comparison of general information between groups
There was no significant difference in age, gender, weight, or height between the two groups (P > 0.05) (Table 1).

Comparison of VAS score for postoperative analgesia between groups
There was no significant difference in VAS scores at rest or while coughing within 2 h postoperation between the two groups (P > 0.05). The VAS scores of the research group at rest were significantly lower within 12 h and 24 h postoperation compared to the control group (P < 0.05). The VAS scores of the research group while coughing were significantly lower within 4 h and 12 h postoperation compared to the control group (P < 0.05) (Table 2).

Comparison of inflammatory factors between groups at different timepoints
There were no significant differences in the levels of serum TNF-α, IL-6, or IL-8 within 2 h postoperation between groups (P > 0.05). Serum TNF-α levels in the research group at 24 h postoperation were significantly lower than the control group (P < 0.05), while those of IL-6 and IL-8 were significantly lower 24 h and 48 h postoperation (P < 0.05) (Table 3).

Comparison of instances of PCIA compression at different timepoints between groups
The number of PCIA compressions within 12 h, 24 h, and 48 h postoperation was significantly lower in the research group compared to the control group (P < 0.05) (Table 4).

Ramsay scores of both groups at different timepoints
The Ramsay scores of the two groups were not significantly different within 12 h, 24 h, or 48 h postoperation (P > 0.05) (Table 5).

Comparison of adverse reactions between groups
Nausea and dizziness (5.00% and 1.67%, respectively) were significantly less frequent in the research group compared to the control group (18.33% and 11.67%, respectively) (P < 0.05). There were no significant differences in the incidences of vomiting, urinary retention, or drowsiness (P > 0.05) (Table 6).
Table 1 Comparison of general data between the two groups

<table>
<thead>
<tr>
<th>General data</th>
<th>Study group, n = 60</th>
<th>Control group, n = 60</th>
<th>t/χ² value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57.7 ± 7.8</td>
<td>55.8 ± 7.1</td>
<td>1.395</td>
<td>0.166</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55.9 ± 5.4</td>
<td>57.0 ± 6.1</td>
<td>-1.046</td>
<td>0.298</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.9 ± 5.2</td>
<td>159.6 ± 6.0</td>
<td>-0.683</td>
<td>0.496</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>122.4 ± 8.4</td>
<td>121.3 ± 7.0</td>
<td>0.779</td>
<td>0.437</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>74.1 ± 6.0</td>
<td>75.6 ± 7.5</td>
<td>-1.210</td>
<td>0.229</td>
</tr>
<tr>
<td>Heart rate (times/min)</td>
<td>81.5 ± 8.0</td>
<td>80.4 ± 8.5</td>
<td>0.730</td>
<td>0.467</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>105.7 ± 16.4</td>
<td>107.1 ± 20.0</td>
<td>-0.419</td>
<td>0.676</td>
</tr>
<tr>
<td>Anesthesia time (min)</td>
<td>124.8 ± 15.0</td>
<td>126.4 ± 14.3</td>
<td>-0.598</td>
<td>0.551</td>
</tr>
<tr>
<td>ASA grade, n (%)</td>
<td></td>
<td></td>
<td>0.616</td>
<td>0.432</td>
</tr>
<tr>
<td>I</td>
<td>39 (65.00)</td>
<td>43 (71.67)</td>
<td>2.596</td>
<td>0.107</td>
</tr>
<tr>
<td>II</td>
<td>21 (35.00)</td>
<td>17 (28.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>11 (18.33)</td>
<td>5 (8.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>49 (81.67)</td>
<td>55 (91.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease, n (%)</td>
<td></td>
<td></td>
<td>1.081</td>
<td>0.298</td>
</tr>
<tr>
<td>Yes</td>
<td>3 (5.00)</td>
<td>6 (10.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>57 (95.00)</td>
<td>54 (90.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>11 (18.33)</td>
<td>17 (28.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>49 (81.67)</td>
<td>43 (71.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td>1.677</td>
<td>0.195</td>
</tr>
<tr>
<td>Disease type, n (%)</td>
<td>22 (36.67)</td>
<td>30 (50.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibroid</td>
<td>16 (26.67)</td>
<td>10 (16.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical carcinoma</td>
<td>12 (20.00)</td>
<td>8 (13.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>10 (16.67)</td>
<td>12 (20.00)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

PCIA is a common postoperative analgesia method that produces transient analgesic effects through the intravenous injection of general anesthesia drugs. Patients can induce the delivery of analgesia according to their own needs; the delivery system is convenient to use, and analgesia is quick in onset[3]. Butorphanol is a mixed-receptor-agonist antagonist that can stimulate the corresponding receptors in the central nervous system to produce dual effects. This drug has several advantages, including the production of a strong, long-lasting analgesic effect with no adverse effects on respiratory function and a low-risk for dependence[16]. Blanco et al[17] found a good analgesic effect with patient-controlled analgesia with dexmedetomidine and butorphanol in patients undergoing hysteroscopic ectopic pregnancy surgery; this drug combination can inhibit the increase in cortisol, adrenocorticotropic hormone, and blood glucose levels and reduce the stress response of the body. However, butorphanol cannot be used in combination with opioids, and its analgesic effect is limited when it is used alone and may lead to nausea, vomiting, lethargy, delirium, and other adverse reactions[18].

Quadratus lumborum block is a trunk nerve block technique that provides good postoperative analgesia for abdominal and lower extremity surgery[19]. One study has shown that the use of quadratus lumborum block in elderly patients after laparoscopic radical resection of rectal cancer reduces the consumption of opioids during general anesthesia, postoperative patient delirium, the consumption of opioids after surgery, and the occurrence of adverse reactions, in addition to yielding good postoperative...
Table 2 Comparison of visual analog scale scores of postoperative analgesia between the two groups (mean ± SD, points)

<table>
<thead>
<tr>
<th></th>
<th>2 h after operation</th>
<th>4 h after operation</th>
<th>12 h after operation</th>
<th>24 h after operation</th>
<th>48 h after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>At resting state</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group (n = 60)</td>
<td>2.29 ± 0.59</td>
<td>2.78 ± 0.81</td>
<td>2.90 ± 0.78</td>
<td>2.45 ± 0.65</td>
<td>1.75 ± 0.63</td>
</tr>
<tr>
<td>Control group (n = 60)</td>
<td>2.15 ± 0.52</td>
<td>3.07 ± 0.85</td>
<td>3.31 ± 0.88</td>
<td>2.81 ± 0.74</td>
<td>1.90 ± 0.50</td>
</tr>
<tr>
<td>t value</td>
<td>1.379</td>
<td>-1.913</td>
<td>-2.701</td>
<td>-2.831</td>
<td>-1.445</td>
</tr>
<tr>
<td>P value</td>
<td>0.171</td>
<td>0.058</td>
<td>0.008</td>
<td>0.005</td>
<td>0.151</td>
</tr>
<tr>
<td>At cough state</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group (n = 60)</td>
<td>2.50 ± 0.64</td>
<td>3.10 ± 0.75</td>
<td>3.08 ± 0.81</td>
<td>2.94 ± 0.86</td>
<td>2.26 ± 0.78</td>
</tr>
<tr>
<td>Control group (n = 60)</td>
<td>2.37 ± 0.59</td>
<td>3.54 ± 0.88</td>
<td>3.51 ± 0.89</td>
<td>3.12 ± 0.90</td>
<td>2.43 ± 0.83</td>
</tr>
<tr>
<td>t value</td>
<td>1.157</td>
<td>-2.948</td>
<td>-2.768</td>
<td>-1.120</td>
<td>-1.156</td>
</tr>
<tr>
<td>P value</td>
<td>0.250</td>
<td>0.004</td>
<td>0.007</td>
<td>0.265</td>
<td>0.250</td>
</tr>
</tbody>
</table>

VAS: Visual analog scale.

Table 3 Comparison of inflammatory factor levels at different times after operation between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Indexes</th>
<th>2 h after operation</th>
<th>24 h after operation</th>
<th>48 h after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α (pg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group (n = 60)</td>
<td>161.5 ± 27.5</td>
<td>228.5 ± 32.4</td>
<td>230.6 ± 35.1</td>
</tr>
<tr>
<td>Control group (n = 60)</td>
<td>157.8 ± 25.3</td>
<td>242.7 ± 29.6</td>
<td>238.2 ± 31.8</td>
</tr>
<tr>
<td>t value</td>
<td>0.767</td>
<td>-2.506</td>
<td>-1.243</td>
</tr>
<tr>
<td>P value</td>
<td>0.445</td>
<td>0.014</td>
<td>0.216</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group (n = 60)</td>
<td>51.77 ± 6.83</td>
<td>89.47 ± 9.20</td>
<td>83.65 ± 8.11</td>
</tr>
<tr>
<td>Control group (n = 60)</td>
<td>54.02 ± 8.16</td>
<td>95.71 ± 10.36</td>
<td>97.20 ± 9.54</td>
</tr>
<tr>
<td>t value</td>
<td>-1.638</td>
<td>-3.489</td>
<td>-8.382</td>
</tr>
<tr>
<td>P value</td>
<td>0.104</td>
<td>0.001</td>
<td>0.000</td>
</tr>
<tr>
<td>IL-8 (pg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group (n = 60)</td>
<td>71.5 ± 13.9</td>
<td>94.6 ± 18.6</td>
<td>88.2 ± 15.7</td>
</tr>
<tr>
<td>Control group (n = 60)</td>
<td>73.6 ± 12.5</td>
<td>102.5 ± 20.4</td>
<td>97.8 ± 16.4</td>
</tr>
<tr>
<td>t value</td>
<td>-0.870</td>
<td>-2.217</td>
<td>-3.275</td>
</tr>
<tr>
<td>P value</td>
<td>0.386</td>
<td>0.029</td>
<td>0.001</td>
</tr>
</tbody>
</table>

IL: Interleukin; TNF-α: Tumor necrosis factor-alpha.

In this study, VAS scores at rest and while coughing and the number of PCIA compressions were used to evaluate the analgesic effect, and the Ramsay score was used to evaluate the sedative effect. It was found that the combination of lumbar block and postoperative PCIA with butorphanol after gynecological surgery under general anesthesia helped to improve the analgesic and sedative effects and reduce the number of PCIA compressions. This is because the quadratus lumborum blocks the injection of local anesthetics between the quadratus lumborum and its surrounding thoracolumbar fascia under the guidance of ultrasound; thus, local anesthetics diffuse to the paravertebral space along the thoracolumbar and intrathoracic fascia and result in an indirect paravertebral block, which has dual analgesic effects on the abdominal wall and viscera. Simultaneously, the sympathetic nerves and receptors sensitive to local anesthetics are distributed in the thoracolumbar fascia, and quadratus lumborum analgesic effects[20].
The inflammatory response is an important factor that causes pain. TNF-α, IL-6, and IL-8 are all classical inflammatory factors. When trauma occurs, mononuclear macrophages activate and release a large amount of TNF-α, which not only causes direct tissue damage but also stimulates the synthesis of proinflammatory factors such as IL-6 and IL-8, causing an increased inflammatory response. In this study, these inflammatory indicators were detected at different timepoints postoperation and showed that quadratus lumborum block combined with butorphanol PCA under general anesthesia can reduce the degree of inflammation in patients after gynecological surgery, which is an important mechanism of pain relief and promotes rehabilitation.

This study also found that quadratus lumborum block combined with butorphanol PCA after gynecological surgery under general anesthesia is beneficial for reducing adverse reactions such as nausea and dizziness. This may be related to a reduction in the numbers of PCA compressions and the dosage of general anesthesia drugs.

Quadratus lumborum block combined with butorphanol PCA in postoperative analgesia for gynecological surgery with general anesthesia not only has application advantages but is closely related to the reduction of inflammation, which has clinical value. However, VAS scores are strongly subjective and are greatly affected by patient tolerance, underlying diseases, and other factors, which may have impacted the results. Thus, it is necessary to identify more objective pain indicators to further prove the analgesic effect of this combination of techniques.

CONCLUSION

In conclusion, after gynecological surgery with general anesthesia, quadratus lumborum block combined with butorphanol PCA significantly improved the analgesic effect and reduced the degree of inflammation, the number of PCA compressions, and the Ramsay scores.

Table 4 Comparison of patient-controlled intravenous analgesia compression times at different times after operation between the two groups (mean ± SD, times)

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>12 h after operation</th>
<th>24 h after operation</th>
<th>48 h after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>60</td>
<td>1.47 ± 0.60</td>
<td>2.18 ± 0.56</td>
<td>2.64 ± 0.62</td>
</tr>
<tr>
<td>Control group</td>
<td>60</td>
<td>3.13 ± 1.02</td>
<td>4.30 ± 0.94</td>
<td>4.16 ± 0.90</td>
</tr>
<tr>
<td>t value</td>
<td></td>
<td>-10.866</td>
<td>-15.008</td>
<td>-10.773</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 5 Ramsay score comparison of two groups at different times after operation (mean ± SD, points)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>12 h after operation</th>
<th>24 h after operation</th>
<th>48 h after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>60</td>
<td>2.40 ± 0.57</td>
<td>2.33 ± 0.60</td>
<td>2.18 ± 0.56</td>
</tr>
<tr>
<td>Control group</td>
<td>60</td>
<td>2.57 ± 0.61</td>
<td>2.50 ± 0.74</td>
<td>2.31 ± 0.68</td>
</tr>
<tr>
<td>t value</td>
<td></td>
<td>-1.577</td>
<td>-1.382</td>
<td>-1.143</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.117</td>
<td>0.170</td>
<td>0.255</td>
</tr>
</tbody>
</table>

Table 6 Comparison of related adverse reactions between the two groups, n (%)
compressions, and adverse reactions.

**ARTICLE HIGHLIGHTS**

**Research background**
Laparoscopic surgery has become a common surgical method for clinical treatment of intra-abdominal lesions.

**Research motivation**
This study explored the role and influence of butorphanol in patient-controlled intravenous analgesia (PCIA) lumbar spine block after general anesthesia gynecological surgery.

**Research objectives**
To explore the possible application prospect of butorphanol in PCIA lumbar block after general anesthesia gynecological surgery.

**Research methods**
The investigation was conducted on 120 female patients who underwent laparoscopic surgery in our hospital from May 2017 to May 2020.

**Research results**
The serum tumor necrosis factor-α levels of the research group 24 h postoperatively were significantly lower than those of the control group ($P < 0.05$). The levels of serum interleukin-6 and interleukin-8 in the study group 24 h and 48 h postoperatively were significantly lower than those in the control group ($P < 0.05$).

**Research conclusions**
PCIA lumbar block with butorphanol after general anesthesia and gynecological surgery can significantly improve the analgesic effect.

**Research perspectives**
Quadratus lumborum block combined with butorphanol postoperative PCIA has significantly better analgesic effects and may be more widely used.

**REFERENCES**


8. Hamanishi J, Mandal M, Matsumura N, Abiko K, Baba T, Konishi I. PD-1/PD-L1 blockade in


Retrospective Study

Teicoplanin combined with conventional vancomycin therapy for the treatment of pulmonary methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* infections

Wei Wu, Min Liu, Jia-Jing Geng, Mei Wang

**ORCID number:** Wei Wu 0000-0002-9277-9124; Min Liu 0000-0002-3574-8487; Jiajing Geng 0000-0002-1082-5159; Mei Wang 0000-0003-4082-3506.

**Author contributions:** Wu W and Wang M designed the research study; Liu M performed the research; Geng JJ analyzed the data and wrote the manuscript.

**Institutional review board statement:** The study was reviewed and approved by the Beijing Tongren Hospital, Capital Medical University Institutional Review Board (Approval No. TRECKY2020-100).

**Informed consent statement:** All study participants provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** No conflict of interest.

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

**Country/Territory of origin:** China

**Specialty type:** Respiratory System

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Abstract**

**BACKGROUND**

Vancomycin and teicoplanin are both antibiotics that have significant antimicrobial effects on Gram-positive cocci.

**AIM**

To explore the value of teicoplanin combined with conventional (vancomycin only) anti-infective therapy for the treatment of methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* pulmonary infections.

**METHODS**

A total of 86 patients with methicillin-resistant *Staphylococcus aureus* or methicillin-resistant *Staphylococcus epidermidis* pulmonary infections, treated in our hospital between January 2018 and February 2020, were assigned to the study and control groups using a random number table method, with 43 patients in each group. The control group received conventional treatment (vancomycin), and the study group received both teicoplanin and conventional treatment. The following indicators were assessed in both groups: the time required for symptom relief, treatment effectiveness, serum levels of inflammatory factors (procalcitonin, interleukin-1β, tumor necrosis factor-α, C-reactive protein), clinical pulmonary infection scores before and after treatment, and the incidence of adverse reactions.

**RESULTS**

Patients in the study group were observed to have faster cough and expectoration resolution, white blood cell count normalization, body temperature normalization, and rales disappearance than patients in the control group (all \( P < 0.05 \));
Pulmonary infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE) are common in our hospital. These infections are typically resistant to treatment with cefradine, oxacillin, or methicillin. In recent years, the incidence of these infections has been rising continuously, and they have become challenges that seriously threaten patients’ lives, health, and prognoses[1-3].

Vancomycin and teicoplanin are important drugs in the clinical treatment of MRSA and MRSE lung infections and have significant antimicrobial effects on Gram-positive cocci. However, the overall efficacy of treatment with vancomycin alone is not good; increasing the dosage to ensure a therapeutic effect also increases the risk of adverse reactions, resulting in a significant limitation to its use as a single-drug treatment[4-6].

Teicoplanin is a novel glycopeptide antibacterial preparation for use in place of vancomycin. This novel drug has enhanced antibacterial activity against MRSA and MRSE due to the addition of fatty acid side chains to its chemical structure, which also increases its molecular mass and half-life, relative to vancomycin[7,8]. Additionally, teicoplanin has a longer dosing interval than vancomycin, which has increased its safety and reduced its risk of adverse events (e.g., renal toxicity and Redman syndrome) compared with vancomycin[9,10].

Thus, we selected 86 patients with pulmonary MRSA or MRSE infections treated in our hospital and compared the treatment outcomes in patients receiving conventional antimicrobial treatment (vancomycin only) with those receiving treatment with vancomycin and teicoplanin.
MATERIALS AND METHODS

Patient population
Patients were eligible to participate in the study if they had pulmonary MRSA or MRSE infections confirmed by lung computed tomography, X-ray examination, and blood cultures, were less than 80 years of age, and agreed to demonstrate good compliance and cooperate throughout the study. Patients were excluded if they had mixed pulmonary infections caused by multiple drug-resistant bacteria species, evidence of immune system dysfunction, an expected survival time of less than 2 wk, kidney or other organ lesions, malignancies, allergies to the study medications, cardiovascular or cerebrovascular diseases, or if they failed to demonstrate compliance throughout the investigation. This study was approved by the ethics committee of our hospital.

Treatment
Patients in both groups received routine interventions after hospitalization, including treatments to reduce expectoration and suppress coughing; supplemental oxygen was also provided. The control group received intravenous vancomycin (0.5 g in 250 mL of normal saline, every 8 h). Peak drug concentrations were measured after 3 d of treatment, and the dosage was adjusted to maintain 5–10 mg/L of vancomycin. Patients in the study group were similarly dosed with vancomycin and also received intravenous teicoplanin (0.4 g in 250 mL of normal saline, every 12 h for 3 d, then once per day for the duration of treatment). Both groups were treated for 7 d.

Indicators
Both groups were monitored to determine the period of time from the beginning of treatment to symptom relief. The indicators of symptom relief were normalization of white blood count and body temperature and the disappearance of cough, expectoration, and rales. We also monitored the patients for lung lesion resolution (resolution of 90% of the lesions was scored as marked effectiveness; resolution of 50%–89% of the lesions was considered effective) using radiography. Thus, the total effectiveness rate was determined as the percentage of patients in each group demonstrating effective and markedly effective outcomes[11]. We also compared the baseline and post-treatment levels of serum inflammatory factors between the groups, including procalcitonin, interleukin-1β, tumor necrosis factor-α, and C-reactive protein; we also assessed the pre- and post-treatment clinical pulmonary infection scores (CPISs). Serum levels of inflammatory markers were determined using appropriate enzyme-linked immunosorbent assays. Finally, the experience of adverse events during treatment was compared between the groups.

Statistical analysis
All statistical analyses were performed using SPSS (version 22.0, SPSS, Chicago, IL, United States). A P value < 0.05 was considered statistically significant. Means were compared using t-tests, and qualitative data (percent values) were compared using the χ² test.

RESULTS
A total of 86 patients with pulmonary MRSA or MRSE infections, treated in our hospital between January 2018 and February 2020, were randomly assigned (using a random number table) to the study and control groups; 43 patients were assigned to each group. The study group comprised 24 men and 19 women. At baseline, the average age of the participants in the study group was 58.59 ± 10.77 (range: 46–71) years, and the average body mass index was 22.19 ± 3.07 (range: 18.2–26.4) kg/m². The average duration of their disease was 6.05 ± 2.13 (range: 2–10) d. The comorbidities among this group included chronic obstructive pulmonary disease (n = 11), coronary heart disease (n = 2), cerebrovascular disease (n = 4), chronic bronchitis (n = 11), and other diseases (n = 2).

The control group included 26 men and 17 women, with an average age of 60.07 ± 11.35 (range: 43–76) years and an average body mass index of 21.95 ± 3.23 (range: 17.8–27.1) kg/m². The average duration of disease in this group was 5.89 ± 2.32 (range: 1–10 d). The comorbidities in this group included chronic obstructive pulmonary disease (n = 10), coronary heart disease (n = 4), cerebrovascular disease (n = 5), chronic
bronchitis (n = 9), and other diseases (n = 4). Based on these baseline data, there were no significant differences between the two groups.

**Time to symptom relief**
In the study group, the routine blood test results returned to normal after treatment, with complete resolution of clinical symptoms. Post-treatment X-ray examinations also showed that > 90% of the lung lesions resolved, indicating marked effectiveness. In the control group, the routine blood test results also returned to normal, the clinical symptoms improved significantly, and the post-treatment X-rays showed an effective rate of 50%–89% for lung lesion resolution.

The study group demonstrated significantly faster cough and expectoration disappearance, white blood count normalization, body temperature normalization, and rales disappearance than the control group (all \( P < 0.05 \); Table 1).

**Treatment effect**
The total effective rate of the study group (93.02%) was higher than that of the control group (76.74%; \( P < 0.05 \) ) (Table 2).

**Serum inflammatory factors and CPISs**
In the study group, the baseline serum levels of the inflammatory factors and the CPISs were similar to those in the control group (Table 3). After treatment, the serum levels of the inflammatory factors and the CPISs were significantly lower than those in the control group (\( P < 0.05 \); Table 3).

**Adverse events**
There was no significant difference in the incidence of adverse events between the study (11.63%) and control (6.98%) groups (\( P > 0.05 \)), as shown in Table 4.

**DISCUSSION**
Pulmonary MRSA and MRSE infections are types of antimicrobial-resistant infections that are common in our hospital and are associated with shock, ventilator use, invasive surgeries, and anesthesia. Most patients with these infections experience some degree of dyspnea, fever, expectoration, and other manifestations[12,13]. Moreover, the incidence of pulmonary infections caused by MRSA and MRSE has continued to increase over recent years due to the increasing frequency of antibiotic misuse. The most effective way of treating these types of infections remains a research hotspot.

The drugs currently used to treat pulmonary infections are glycopeptide antibacterial agents, including the wide use of vancomycin, a drug that inhibits bacterial cell wall synthesis by stopping the synthesis of the cell wall glycopeptide polymerase[14]. Vancomycin has a significant antibacterial effect on Gram-positive bacteria, especially Staphylococcus epidermidis and Staphylococcus aureus. However, it also has a nephrotoxic effect on the patient. The administration frequency of this drug should be kept as low as possible, particularly in elderly patients and those with other severe illnesses, to reduce the drug’s kidney toxicity[15].

Teicoplanin is another important drug used in the clinical treatment of pulmonary infections and is also a novel glycopeptide antibacterial agent. Compared with vancomycin, the peptide skeleton of teicoplanin contains additional fatty acid side chains, which have a 90% binding rate to serum albumin and high lipophilicity. This characteristic of this drug promotes the absorption of the drug by tissues and cells[16]. Sezai et al[17] used vancomycin and teicoplanin to treat patients with MRSA pulmonary infections and demonstrated complete bacterial clearance in 87.80% (a total effective rate of up to 90.24%) of the patients in the test group, which was significantly higher than the 68.29% with complete clearance in the control group. The patients in the test group also demonstrated significantly lower post-treatment serum procalcitonin and C-reactive protein levels than before treatment. Ogawa et al[18] also confirmed that the application of high-dose teicoplanin can effectively downregulate the levels of inflammatory factors and improve bacterial clearance in patients with pulmonary MRSA infections.

Compared with our conventional (vancomycin only) treatment, treating pulmonary MRSA and MRSE infections with vancomycin and teicoplanin resulted in a higher total effective rate than for the conventional treatment. These results are consistent with the results of the above-mentioned studies. In addition, the time to symptom relief was shorter than in the control group, and the post-treatment CPISs were lower.
Table 1 Average symptom relief time for patients treated with either vancomycin only or vancomycin and teicoplanin (mean ± SD)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Vancomycin only</th>
<th>Vancomycin + teicoplanin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough and expectoration resolution (d)</td>
<td>8.29 ± 2.15</td>
<td>6.12 ± 1.56</td>
<td>0.000</td>
</tr>
<tr>
<td>WBC normalization (d)</td>
<td>8.68 ± 2.44</td>
<td>6.77 ± 2.13</td>
<td>0.000</td>
</tr>
<tr>
<td>Body temperature normalization (d)</td>
<td>5.68 ± 1.18</td>
<td>4.07 ± 1.09</td>
<td>0.000</td>
</tr>
<tr>
<td>Rales resolution (d)</td>
<td>8.89 ± 2.02</td>
<td>6.64 ± 1.43</td>
<td>0.000</td>
</tr>
</tbody>
</table>

WBC: White blood cell count.

Table 2 Treatment effects for patients treated with vancomycin (only) or vancomycin and teicoplanin, n (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Markedly effective</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>43</td>
<td>26 (60.47)</td>
<td>14 (32.56)</td>
<td>3 (6.98)</td>
<td>40 (93.02)</td>
</tr>
<tr>
<td>Control group</td>
<td>43</td>
<td>18 (41.86)</td>
<td>15 (34.88)</td>
<td>10 (23.26)</td>
<td>33 (76.74)</td>
</tr>
<tr>
<td>χ² value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.441</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.035</td>
</tr>
</tbody>
</table>

Table 3 Inflammation marker levels in patients treated with vancomycin (only) or vancomycin and teicoplanin

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>PCT (ng/mL)</th>
<th>IL-1β (pg/mL)</th>
<th>TNF-α (pg/mL)</th>
<th>CRP (mg/L)</th>
<th>CPIS (point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group</td>
<td>43</td>
<td>0.86 ± 0.23</td>
<td>223.37 ± 36.25</td>
<td>139.74 ± 23.65</td>
<td>91.39 ± 10.68</td>
<td>7.69 ± 2.88</td>
</tr>
<tr>
<td>Control group</td>
<td>43</td>
<td>0.91 ± 0.20</td>
<td>219.29 ± 35.56</td>
<td>142.91 ± 20.88</td>
<td>89.24 ± 12.29</td>
<td>8.01 ± 3.04</td>
</tr>
<tr>
<td>t value</td>
<td></td>
<td>1.076</td>
<td>0.527</td>
<td>0.659</td>
<td>0.866</td>
<td>0.501</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.285</td>
<td>0.600</td>
<td>0.512</td>
<td>0.389</td>
<td>0.618</td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group</td>
<td>43</td>
<td>0.28 ± 0.03</td>
<td>141.18 ± 18.62</td>
<td>41.46 ± 9.08</td>
<td>11.76 ± 4.43</td>
<td>2.19 ± 0.79</td>
</tr>
<tr>
<td>Control group</td>
<td>43</td>
<td>0.34 ± 0.05</td>
<td>163.53 ± 23.84</td>
<td>50.96 ± 10.35</td>
<td>18.25 ± 5.39</td>
<td>3.87 ± 1.01</td>
</tr>
<tr>
<td>t value</td>
<td></td>
<td>6.748</td>
<td>4.845</td>
<td>4.525</td>
<td>6.100</td>
<td>8.591</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

CPIS: Clinical pulmonary infection score; CRP: C-reactive protein; IL-1β: Interleukin-1β; PCT: Procalcitonin; TNF-α: Tumor necrosis factor-α.

Table 4 Adverse events experienced by patients treated with vancomycin (only) or with vancomycin and teicoplanin, n (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Gastrointestinal reaction</th>
<th>Dizziness and headache</th>
<th>Vomiting and nausea</th>
<th>Total incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>43</td>
<td>2 (4.65)</td>
<td>1 (2.33)</td>
<td>2 (4.65)</td>
<td>5 (11.63)</td>
</tr>
<tr>
<td>Control group</td>
<td>43</td>
<td>0 (0.00)</td>
<td>2 (4.65)</td>
<td>1 (2.33)</td>
<td>3 (6.98)</td>
</tr>
<tr>
<td>χ² value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.551</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.458</td>
</tr>
</tbody>
</table>

than those in the control group. However, there was no significant difference in the incidence of adverse reactions between the two groups. This indicates that combining teicoplanin and vancomycin treatments in patients with pulmonary MRSA and MRSE infections can effectively improve the treatment effect, relative to the conventional treatment, while ensuring patient safety.
We believe that the additional benefit provided by teicoplanin can be explained as follows. The main antibacterial mechanism of teicoplanin is its ability to inhibit transglycosylation during bacterial cell wall synthesis, thereby damaging the integrity and strength of the cell wall. This results in bacterial growth inhibition and the ultimate killing of the bacteria. Teicoplanin demonstrates strong tissue penetration, high protein binding, and a long half-life. Therefore, even once-daily administration can maintain an ideal blood concentration and bioavailability. Some studies also indicate that good lipophilic properties of teicoplanin facilitate drug penetration into tissues and cells. Thus, the drug effectively regulates the transfer of disaccharides and peptides required for cell wall mucins and stops cell wall biosynthesis, thereby promoting bacterial death.

Furthermore, procalcitonin, interleukin-1β, tumor necrosis factor-α, and C-reactive protein are indicators of the degree of inflammatory response in the body. Inflammation can increase the permeability of vascular endothelial cells, promote the exudation of numerous inflammatory substances from tissues, and aggravate the disease. In this study, the levels of these inflammatory indicators in the study group were significantly lower than in the control group after treatment. These results indicate that teicoplanin has high value in the treatment of pulmonary MRSA and MRSE infections in part because it downregulates the inflammatory response.

CONCLUSION
Our study demonstrated that, compared to conventional therapy, the combined teicoplanin/vancomycin treatment of patients with pulmonary MRSA and MRSE infections results in improved clinical responses, regulates the levels of serum inflammatory factors, and improves the disease treatment effect, without increasing the risk of adverse events.

ARTICLE HIGHLIGHTS

Research background
Vancomycin and teicoplanin are important drugs in the clinical treatment of methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* lung infections.

Research motivation
Single-drug treatment of lung infections is not effective.

Research objectives
We want to compare the therapeutic effects of conventional antibacterial therapy (vancomycin only) and vancomycin plus teicoplanin.

Research methods
We selected 86 patients with methicillin-resistant *Staphylococcus aureus* (MRSA) or *Staphylococcus epidermidis* lung infections and divided them into a study group and a control group, with 43 cases in each group.

Research results
The study group was more effective than the control group.

Research conclusions
The combined teicoplanin/vancomycin treatment of patients with pulmonary methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* infections resulted in improved clinical responses.
Research perspectives
The combined application of antibacterial drugs increases the cure rate of the disease.

REFERENCES


18. Ogawa R, Kobayashi S, Sasaki Y, Makimura M, Echizen H. Population pharmacokinetic and...


Retrospective Study

Application of narrative nursing in the families of children with biliary atresia: A retrospective study

Liang-Hui Zhang, Hong-Yan Meng, Ren Wang, You-Cheng Zhang, Jian Sun

Abstract

BACKGROUND
Narrative nursing is an important clinical nursing intervention model. It is the practice of patient storytelling to share the essence of nursing. The current clinical intervention for biliary atresia (BA) mainly focuses on disease treatment and does not pay enough attention to the psychological state of family members.

AIM
To explore the application value of narrative nursing in the families of children with BA.

METHODS
Sixty-four family members of children with BA in our hospital from December 2017 to October 2020 were retrospectively included and were divided into a study group (n = 32) and a control group (n = 32). The control group was provided with routine nursing, while the study group was given narrative nursing on the basis of the control group. The scores of mood state (depression and anxiety), family members’ nursing ability, perceived stress, and nursing job satisfaction of the children’s families were calculated before and after the intervention.

RESULTS
Before intervention, there was no significant difference in the self-rating anxiety scale and self-rating depression scale scores between groups (P > 0.05). After intervention, the self-rating anxiety scale and self-rating depression scale scores in the study group were lower than those in the control group (both P = 0.000). Before intervention, the study group adjusted life to meet care needs, evaluated family members and social resources, dealt with personal emotions, responded to needs, and provided assistance, and the adaptive care role scores were not significantly different from those in the control group (P = 0.802, 0.819, 0.694, 0.796, and 0.686, respectively). After intervention, all scores were significantly
lower in the study group than in the control group (all $P < 0.0001$). Before intervention, there was no significant difference in the child post-traumatic stress disorder symptom score (CPSS) score between groups ($P = 0.615$). After intervention, the CPSS scores were significantly lower than those before intervention in both groups and lower in the study group than in the control group ($P < 0.0001$). Nursing job satisfaction of the family members of the study group (93.75%) was higher than that of the control group (75.00%) ($P = 0.039$).

CONCLUSION

Narrative nursing with family members of children with BA can effectively alleviate negative emotions, reduce perceptual pressure, and improve nursing ability. Additionally, family members are more satisfied with nursing work.

Key Words: Narrative nursing; Biliary atresia; Negative emotions; Nursing ability; Retrospective study; Perceptual pressure

Core Tip: This paper verified the positive effect of narrative nursing on children with congenital biliary atresia. The intervention of narrative nursing to the family members of children with biliary atresia can effectively alleviate their negative emotion, reduce the perceptual pressure, and improve their nursing ability.

INTRODUCTION

Biliary atresia (BA) is a common clinical disease with a high incidence in children. Moreover, in most children, BA is accompanied by jaundice, which is a great threat to the child’s physical and mental health and quality of life[1-5]. Surgery is an important measure for the clinical treatment of BA, in which hepatopancreaticojejunostomy is most commonly used[6-8]. However, approximately 60% of children still require liver transplantation before the age of 20 years, and portal hypertension, nutritional dysplasia, and liver cirrhosis have a large impact on the long-term survival rate[9-12].

Most family members of children with BA experience serious anxiety and depression. In addition, serious cases can produce many extreme behaviors, such as abandoning of the child and causing secondary harm to the child. Meanwhile, the current clinical intervention for BA mainly focuses on disease treatment and does not pay enough attention to the psychological state of family members. This can lead to the failure of long-term standardized treatment and reexamination. In addition, it has a significant impact on the favorable outcomes of the disease. Consequently, the development of effective nursing interventions for the families of children with BA has become a research hotspot. Nursing interventions can not only regulate the physical and mental state of the child’s family members, it is also of great significance to ensure the improvement of the child’s disease.

As an important clinical nursing intervention model, nurses mainly use narrative nursing to help them reconstruct the meaning of life and disease stories by listening to and absorbing the stories of the intervention subjects. Moreover, it helps them to discover the main points of nursing during the intervention period to achieve the intervention effect[13,14].

Consequently, 64 family members of children with BA in our hospital were selected and divided into two groups (control group and study group) to explore the application value of narrative nursing.
MATERIALS AND METHODS

General information
A total of 64 family members of children with digital BA in our hospital from December 2017 to October 2020 were retrospectively included and were divided into two groups: Study group (n = 32) and control group (n = 32). In the study group, there were 17 male and 15 female participants, the age at admission ranged from 3 to 136 d, the average age was 82.97 ± 12.23 d, the range of body mass was 3.0 to 5.8 kg, and the average body mass was 4.40 ± 1.11 kg. Family members of the study group included 19 women and 13 men, aged 24–41 years with an average age of 32.56 ± 5.69 years. Their education level was junior middle school (n = 8), senior high school (n = 13), and junior college and above (n = 11). Regarding the education level, 8 of the family members were in junior middle school, 13 were in senior high school, and 11 were in junior college and above. The average monthly income of the family was < 3000 Yuan in 7 cases, 3000-5000 Yuan in 15 cases, and > 5000 Yuan in 10 cases.

In the control group, there were 19 male and 13 female patients; the age at admission ranged from 31 to 133 d; the average age was 81.91 ± 11.59 d, and their body mass was 3.2 to 5.7 kg (average body mass, 4.32 ± 1.07 kg). Family members of the control group included 21 women and 11 men with an average age of 33.21 ± 6.02 years. The education level was junior middle school (n = 6), senior high school (n = 16), and junior college and above (n = 10). The per capita monthly income of the family was < 3000 Yuan (n = 6), 3000-5000 Yuan (n = 17), and > 5000 Yuan (n = 9). Clinical data such as sex, age, body mass, education level, and per capita monthly income of the family were comparable between the two groups (P > 0.05).

Selection criteria
The inclusion criteria were as follows: (1) presence of lighter stool and yellow skin in the patient; (2) hepatomegaly was found on physical examination; (3) the family members of the children were educated till junior high school or above; (4) they were aware of this study and signed the consent form; and (5) the diagnosis was confirmed by magnetic resonance cholangiography, B-ultrasound, and intraoperative cholangiography. The exclusion criteria were as follows: (1) family members’ occupation in the medical field; (2) hearing impairment, cognitive impairment, speech communication disorder, and nervous system disease; and (3) children with immune system diseases or a blood coagulation disorder.

Methods
The control group underwent routine nursing, routine fasting, gastrointestinal decompression after surgery, and intravenous infusion of nutrient solutions for nutritional support. In addition, regular checks of the gastric tube, catheter, and subhepatic drainage tube were conducted to avoid compression or bending. The child’s head was raised approximately 45° off the bed after waking up, followed by close monitoring of the vital signs, surgical incision, and so forth. If there were conditions such as abdominal distension, abnormal heart rate, restlessness, and abnormal blood pressure fluctuation, the doctor was immediately informed and assisted with the corresponding measures.

The corresponding treatment is given according to the degree of pain in children. Relieving pain by playing soothing music, stroking children, and other measures for those with mild pain were used. If the pain was strong, administration of drug sedation and analgesia was performed, and the defecation frequency, character, and color were strictly observed. The family members of the patients were given a detailed explanation of the pathogenesis, treatment, and prognosis of BA through health education with the intention to alleviate the negative emotions caused by the disease.

Narrative nursing was adopted, and experienced nurses were selected to set up an intervention group based on the control group. First, training for the relevant contents of narrative nursing was performed, and nursing interventions were carried out after the training was complete.

Preparation stage: Nurses fully understood the basic information and condition of the children and actively communicated with the children’s families with an attitude of respect, humility, and empathy, with the intention to gain their trust and establish a harmonious nurse-patient relationship with the family members of the children.

Enter the story of the child: The nurse had a face-to-face conversation with the family without standard or frame, which was mainly based on receptive language and an open interview format, with questions such as “how do you understand the
knowledge related to BA?”, “What was your initial understanding of BA?”, and “How is your sleep?”. Nurses were instructed to smile and give an appropriate response to the family members’ complaints in the process of conversation, intending to guide the family members to talk fully about themselves to understand comprehensively the current serious problems, including the psychological problems, of the children’s families.

**Externalization and deconstruction of the problem:** The nurses were instructed to separate the problem from the family members of the children, help them to extract and name the problems that seriously trouble themselves, and strengthen the family members’ awareness that the problems had nothing to do with themselves. In addition, they discussed the family members’ control over the problem and their courage to deal with the problem so that the members could examine their stories more objectively. Second, we aimed to explore the impact of the problem on itself and others through deconstruction to ask the context of the analytical problem so as to increase its psychological space.

**Looking for exceptions:** The family members were guided to look for life outside the problem and to find the positive events that were ignored by them in the story. The positive force and positive identity implied are worthy of in-depth excavation. The goal was to let the family members of children think that they have the resources and abilities to solve the problem through this process.

**Reconstruct the story:** Transferring the positive power and identity hidden in the exceptional events to the practical problems that plague the patients and provide them with new choices to change the behavior and self-cognition of the children’s families in order to reconstruct the meaning of life. For example, the head nurse in the ward had a face-to-face conversation with a parent to help them name the problem that seriously besieged them as “unfair” in the process of the intervention as a mother who abandoned a child because of great life and ideological pressure. In addition, we demonstrated the impact of “unfairness” on the family members and others around them. Second, we looked for exceptional events, excavating the fragments neglected by the family members, and let them fully realize that they also have the resources and abilities to solve problems. Finally, the hidden positive forces were transferred to practical problems and alternative stories were developed: "despite great pressures in life, they could still continue to treat children through their own efforts and outside help, including the use of drip funding platforms, charitable funds, and so on. In addition, family members achieved psychological satisfaction, soul sublimation, and so on from the children’s attachment to the mother’s eye contact and body language. It was intended to improve the possibilities and opportunities to reconstruct a new life.

**Data evaluation**

The scores of mood state (depression and anxiety) of the two groups before and after the intervention were evaluated using the self-rating depression scale (SDS) and self-rating anxiety scale (SAS) scales: Mild depression: SDS score 53-62, moderate depression: 63-72, severe depression: ≥ 73; mild anxiety: SAS: 50-59, moderate anxiety: 60-69, severe anxiety: ≥ 69.

The scores of the care ability of family members of the two groups before and after the intervention were evaluated according to the caregiver care ability scale (FCTI), including adjusting life to meet care needs, evaluating family and social resources, dealing with personal emotions, responding to needs and providing assistance, and adapting to the role of care. Each dimension included five items, and each item was scored 0, 1, and 2 according to no difficulty, difficulty, and very difficult.

The perceived stress of the two groups before and after intervention was evaluated using the child post-traumatic stress disorder symptom scale (CPSS), and the score of five grades was 43-56 for excessive pressure, 29-42 for obvious pressure, and 0-28 for mild stress.

Finally, the nursing job satisfaction of the family members of the two groups was assessed, and the nursing attitude and nursing quality were evaluated using a self-made nursing job satisfaction questionnaire, with a total of 10 points: Very satisfactory, ≥ 9 points; satisfaction, 7-8 points; dissatisfaction, ≤ 7 points. Nursing job satisfaction was very satisfactory rate + satisfaction rate.

**Statistical analysis**

The data were analyzed using SPSS22.0 (Armonk, NY, United States). Measurement data were described as mean ± SD and then analyzed with the Student’s t-test.
counting data were described as the frequency and constituent ratio (%) and then tested using the \( \chi^2 \) test. In addition, a non-parametric test was used to compare measurement data that did not meet the normal distribution. \( P < 0.05 \) indicated that the difference was statistically significant.

**RESULTS**

**Self-rating anxiety and depression scale scores**
There was no significant difference in the SAS and SDS scores between the study and control groups before the intervention (\( P = 0.662 \) and \( 0.757 \), respectively). The SAS and SDS scores in the study group were lower than those in the control group after the intervention (both \( P < 0.0001 \); Table 1).

**FCTI score**
The study group scores for adjusted life to meet care needs (4.15 ± 1.13), evaluated family members and social resources (3.99 ± 1.24), dealt with personal emotions (3.68 ± 0.99), responded to needs and provided assistance (3.77 ± 1.35), and adaptive care role (3.84 ± 1.26) were not significantly different from the control group score before the intervention (4.22 ± 1.09, \( P = 0.802 \); 4.06 ± 1.19, \( P = 0.819 \); 3.78 ± 1.03, \( P = 0.694 \); 3.86 ± 1.42, \( P = 0.796 \); and 3.97 ± 1.30, \( P = 0.686 \), respectively).

After the intervention, the abovementioned scores for the study group were significantly lower than those in the control group (2.00 ± 0.83 vs 3.08 ± 0.77, 1.65 ± 0.59 vs 2.44 ± 0.63, 1.13 ± 0.47 vs 2.05 ± 0.53, 1.79 ± 0.64 vs 2.82 ± 0.70, and 1.24 ± 0.62 vs 2.27 ± 0.66, respectively; all \( P < 0.0001 \); Table 2).

**CPSS score**
There was no significant difference in the CPSS scores between the study group and the control group before the intervention (\( P = 0.615 \)). However, after the intervention, the CPSS scores of the two groups were lower than those before the intervention (study group: 21.97 ± 2.51 vs 39.64 ± 4.46, \( P = 0.000 \); control group: 28.21 ± 3.35 vs 40.14 ± 3.39, \( P < 0.0001 \)). In addition, after the intervention the study group score was significantly lower than that in the control group (\( P = 0.000 \); Table 3).

**Nursing job satisfaction of children’s family members**
The nursing job satisfaction of the family members of the study group (93.75%) was significantly higher than that of the control group (75.00%) (\( P = 0.039 \); Table 4).

**DISCUSSION**
The pathogenic factors of BA are complex and harmful; it not only causes great pain to the children themselves but also places heavy psychological and economic burdens on the children’s families, leading to negative coping strategies\[15,16\]. In addition, many clinical studies have examined safe and effective treatments for BA; however, most ignore the influence of the caregiver’s psychological state on the disease, which can result in poor communication and coordination, thus affecting the treatment and rehabilitation of the children. Consequently, there is an urgent need to find an intervention measure that can effectively improve the physical and mental state of children’s families.

Narrative nursing is a type of nursing intervention that uses narrative means to help the intervention subject abandon their previous life story and reconstruct a new story with a positive meaning\[17,18\]. The narrative nursing was defined as follows: Nurses listen to the disease stories of the intervention subjects through interviews, summarize and reflect on the stories, assist them in reconstructing the meaning of the disease or their life stories, and clarify the focus of nursing intervention to provide effective, scientific, and reasonable intervention programs for the intervention subjects. In addition, after the intervention of narrative nursing for the care families of critically ill intensive care unit patients, their degree of anxiety was effectively alleviated, and their satisfaction with nursing work was higher. In our study, the SDS, SAS, and CPSS scores in the study group were lower than those in the control group after using the intervention of narrative nursing for family members of children with BA in our hospital. This finding is consistent with the research results of the above scholars, indicating that narrative nursing can effectively relieve the negative emotions and
Zhang LH et al. Narrative nursing in children’s biliary atresia

**Table 1 Comparison of self-rating anxiety and depression scale scores between the two groups (mean ± SD)**

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>SAS</th>
<th>SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group</td>
<td>32</td>
<td>58.91 ± 5.04</td>
<td>60.79 ± 6.27</td>
</tr>
<tr>
<td>Control group</td>
<td>32</td>
<td>59.50 ± 5.68</td>
<td>61.28 ± 6.35</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>0.440</td>
<td>0.311</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.662</td>
<td>0.757</td>
</tr>
<tr>
<td>After intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group</td>
<td>32</td>
<td>43.34 ± 4.60</td>
<td>45.65 ± 5.41</td>
</tr>
<tr>
<td>Control group</td>
<td>32</td>
<td>50.59 ± 5.31</td>
<td>52.23 ± 5.69</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>5.838</td>
<td>4.741</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*P < 0.0001 between group t-test after intervention. SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

**Table 2 Comparison of caregiver care ability scale scores between the two groups (mean ± SD)**

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Adjust life to meet care needs</th>
<th>Assess family and social resources</th>
<th>Deal with personal emotions</th>
<th>Respond to needs and provide assistance</th>
<th>Adapt to the role of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group</td>
<td>32</td>
<td>4.15 ± 1.13</td>
<td>3.99 ± 1.24</td>
<td>3.68 ± 0.99</td>
<td>3.77 ± 1.35</td>
<td>3.84 ± 1.26</td>
</tr>
<tr>
<td>Control group</td>
<td>32</td>
<td>4.22 ± 1.09</td>
<td>4.06 ± 1.19</td>
<td>3.78 ± 1.03</td>
<td>3.86 ± 1.42</td>
<td>3.97 ± 1.30</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>0.252</td>
<td>0.230</td>
<td>0.396</td>
<td>0.260</td>
<td>0.406</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.802</td>
<td>0.819</td>
<td>0.694</td>
<td>0.796</td>
<td>0.686</td>
</tr>
<tr>
<td>After intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group</td>
<td>32</td>
<td>2.00 ± 0.83</td>
<td>1.65 ± 0.59</td>
<td>1.13 ± 0.47</td>
<td>1.79 ± 0.64</td>
<td>1.24 ± 0.62</td>
</tr>
<tr>
<td>Control group</td>
<td>32</td>
<td>3.08 ± 0.77</td>
<td>2.44 ± 0.63</td>
<td>2.05 ± 0.53</td>
<td>2.82 ± 0.70</td>
<td>2.27 ± 0.66</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>5.396</td>
<td>5.178</td>
<td>7.347</td>
<td>6.143</td>
<td>6.434</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.000*</td>
<td>0.000*</td>
<td>0.000*</td>
<td>0.000*</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

*P < 0.0001 between group t-test after intervention.

The survival rate of high-risk BA infants is increasing with the rapid development of the social economy and the continuous improvement of medical care. However, the accompanying diseases also seriously perplex the families of children with BA. Among them, the psychological state of the family of child with BA is complicated, and there are negative emotions such as remorse, depression, despair, helplessness, and contradiction, which can take a toll both emotionally and economically. Medical staff have the responsibility to help the family members to understand correctly the disease and the treatment involved, to provide necessary psychological counseling and effective psychological interventions, to promote parents to cooperate with treatment, and to improve their mental health level. Narrative nursing can create a suitable platform for children’s families to vent their emotions, shorten the distance between nurses and patients, ensure that the stories of the children and their families are fully listened to, and effectively relieve bad emotions.

Additionally, the problems faced by family members are separated from the children and the parents themselves so that they can look at the problem objectively...
Table 3 Comparison of child post-traumatic stress disorder symptom scores between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>32</td>
<td>39.64 ± 4.46</td>
<td>21.97 ± 2.51</td>
<td>19.531</td>
<td>0.000*</td>
</tr>
<tr>
<td>Control group</td>
<td>32</td>
<td>40.14 ± 3.39</td>
<td>28.21 ± 3.35</td>
<td>14.160</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

*P = 0.000 vs before intervention.

Table 4 Comparison of nursing job satisfaction of family members of children in the two groups, n (%)

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Very satisfied</th>
<th>Satisfied</th>
<th>Dissatisfied</th>
<th>Total satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>32</td>
<td>21 (65.63)</td>
<td>9 (28.13)</td>
<td>2 (6.25)</td>
<td>30 (93.75)</td>
</tr>
<tr>
<td>Control group</td>
<td>32</td>
<td>13 (40.63)</td>
<td>11 (34.38)</td>
<td>8 (25.00)</td>
<td>24 (75.00)</td>
</tr>
</tbody>
</table>

χ² = 4.267

P value = 0.039*

*P < 0.05 vs control group.

Therefore, narrative nursing can mobilize the potential and positive characteristics of children’s families by tapping into the flash events neglected by parents and the positive forces hidden behind them. This approach intends to make them strive to develop alternative stories and increase the possibility and opportunity to reconstruct a new life.

Moreover, the care ability of the main caregivers of family members is an important prerequisite and a basis for determining the quality of patient care. The stronger the ability of the main caregivers of the patients’ families, the easier it is to deal with the problems encountered during the care period. Finally, it improves the quality-of-care services for children.

Care ability involves many aspects that are difficult to quantify. Some studies refer to a self-designed scale, which lacks rationality and science. However, the FCTI effectively quantifies the caregiver’s care ability and evaluates family care ability systematically and comprehensively in five dimensions. The results showed that after the intervention, the scores of adjusting life to meet care needs, evaluating family and social resources, dealing with personal emotions, responding to needs and providing assistance, and adapting to the role of care in the study group were significantly lower in the study group than those in the control group. This result indicated that narrative nursing also has a significant advantage in improving the care ability of family members of children with BA, probably because the nursing program can effectively alleviate their negative emotions. Thus, family members are encouraged to actively face the disease and the treatment of their children, gradually accept the reality of the disease, and promote their own ability to take care of their children. In addition, the results showed that the nursing satisfaction of family members of the study group was higher than that of the control group. This result suggests that narrative nursing can also effectively deepen the recognition of nursing work for children with BA, help to reduce nurse-patient disputes, and establish a high-quality service image of the hospital.

CONCLUSION

Generally, narrative nursing interventions for family members of children with BA can effectively alleviate their negative emotions, reduce perceptual pressure, and improve their nursing ability. In addition, family members were more satisfied with the nursing work.
ARTICLE HIGHLIGHTS

Research background
At present, the clinical treatment of biliary atresia (BA) does not pay enough attention to the psychological state of family members.

Research motivation
This study ensures the psychological status of family members of children with BA during treatment.

Research objectives
This study aimed to explore the application value of narrative nursing in children with BA.

Research methods
Sixty-four family members of children with BA were included. The scores of mood state (depression and anxiety), family members’ nursing ability, perceived stress, and nursing job satisfaction of the children’s families were calculated before and after the intervention.

Research results
After the intervention, the child post-traumatic stress disorder symptom scores of the two groups were significantly lower than before the intervention, and the study group was lower than the control group; the nursing job satisfaction of family members in the study group was also significantly higher than that of the control group.

Research conclusions
Narrative nursing for the families of children with BA can effectively alleviate their negative emotions, reduce perceived pressure, improve nursing ability, and make family members more satisfied with nursing work.

Research perspectives
Narrative nursing will be more widely used in the treatment of children with BA.

REFERENCES


Observational Study

Comparative study for predictability of type 1 gastric variceal rebleeding after endoscopic variceal ligation: High-frequency intraluminal ultrasound study

Jeong Hwan Kim, Won Hyeok Choe, Sun-Young Lee, So Young Kwon, In-Kyung Sung, Hyung Seok Park

ORCID number: Jeong Hwan Kim 0000-0002-2503-2688; Won Hyeok Choe 0000-0002-8019-5412; Sun-Young Lee 0000-0003-4146-6686; So Young Kwon 0000-0003-4290-1900; In-Kyung Sung 0000-0003-4290-1950; Hyung Seok Park 0000-0003-3141-4858.

Author contributions: Kim JH and Choe WH contributed to study conception and design; Kim JH, Choe WH, and Kwon SY contributed to collection of clinical data; Kim JH, Choe WH, Kwon SY, Lee SY, Sung IK, and Park HS contributed to data acquisition, data analysis, and interpretation; Kim JH, Choe WH, Kwon SY, Lee SY, Sung IK, and Park HS contributed to writing of the article, editing, reviewing, and final approval of the article.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board of Konkuk University Hospital (KUH1010094).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained from the Electronic Health Records System.

Jeong Hwan Kim, Won Hyeok Choe, In-Kyung Sung, Department of Internal Medicine, Konkuk University School of Medicine, Konkuk University Medical Center, Seoul 05030, South Korea

Sun-Young Lee, Department of Internal Medicine, Konkuk University Medical Center, Seoul 143729, South Korea

So Young Kwon, Department of Internal Medicine, Konkuk University School of Medicine, Seoul 05030, South Korea

Hyung Seok Park, Department of Internal Medicine, Digestive Disease Center, Konkuk University School of Medicine, Seoul 05030, South Korea

Corresponding author: Won Hyeok Choe, MD, PhD, Professor, Department of Internal Medicine, Konkuk University School of Medicine, Konkuk University Medical Center, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, South Korea. 20050101@kuh.ac.kr

Abstract

BACKGROUND
The efficacy of endoscopic ultrasonography for the follow-up of gastric varices treated with endoscopic variceal ligation (EVL) has not been established.

AIM
To evaluate the diagnostic correlation of esophagogastroduodenoscopy (EGD) and high-frequency intraluminal ultrasound (HFIUS) for type 1 gastric varices (GOV1) after EVL and to identify the predictability for rebleeding of EGD and HFIUS.

METHODS
In liver cirrhosis patients with GOV1, we performed endoscopic follow-up using EGD and HFIUS synchronously after EVL for hemorrhage from GOV1. Endoscopic grading and red color signs were analyzed using EGD, and the largest variceal cross-sectional areas were measured using HFIUS. In addition, 1-year follow-up was performed. Variceal rebleeding was defined as the presence of hematemesis, hematochezia, or melena without other evidence of bleeding on endoscopic follow-up.
Endoscopic variceal ligation (EVL) was introduced in the 1980s as an alternative to endoscopic injection sclerotherapy[1]. Several prospective trials reported that EVL was superior to endoscopic injection sclerotherapy in that it eradicated varices more rapidly with less recurrent bleeding and fewer complications[2–7]. Thus, EVL has become the endoscopic treatment of choice for both the control of acute bleeding and the prevention of rebleeding from esophageal varices (EV)[8].

Gastric varices (GVs) are commonly categorized based on their location in the stomach and their relationship with EVs[9,10]. Type 1 gastric varices (GOV1) are the most common subtype of GV and constitute an extension of EV along the lesser curvature of the stomach[9,11]. Because they are considered a continuation of EV, current recommendations have emphasized that GOV1 should be treated as EV. In contrast, the other subtypes of GV, such as IGV1 (varices in the gastric fundus), IGV2 (ectopic varices around the pylorus), and GOV2 (varices extending along the greater curvature toward the gastroduodenal junction), do not respond well to therapeutic modalities used for EV[11–13].

After successful control of acute bleeding with emergency EVL, endoscopic follow-up should be repeated, and residual or recurrent varices should be treated with elective EVL to prevent variceal rebleeding if indicated[12,13]. Esophagogastroduodenoscopy (EGD) is the best practical modality for the follow-up of EV after EVL[12]. However, little is known about whether it is an effective modality for post-EVL endoscopic follow-up of GOV1.

Recently, endoscopic ultrasound (EUS) has been introduced as an important modality in the diagnosis of varices[15,16]. In particular, high-frequency intraluminal ultrasound (HFIUS) has been reported to enable quantitative measurement of variceal

### RESULTS

In 26 patients with GOV1, variceal cross-sectional areas on HFIUS of GOV1 was poorly correlated with EGD grading of GOV1 ($r = 0.36$). In 17 patients who completed 1-year follow-up, variceal cross-sectional areas on HFIUS was a good predictor of subsequent rebleeding, whereas EGD grading was not a predictor of subsequent rebleeding.

### CONCLUSION

HFIUS measurement is more predictive of GOV1 rebleeding than EGD grading, so HFIUS measurement may be necessary for endoscopic follow-up after EVL in patients with GOV1.

### Key Words:
Endoscopic variceal ligation; Esophagogastroduodenoscopy; High-frequency intraluminal ultrasound; Rebleeding; Type 1 gastric varices

Citation: Kim JH, Choe WH, Lee SY, Kwon SY, Sung IK, Park HS. Comparative study for predictability of type 1 gastric variceal rebleeding after endoscopic variceal ligation: High-frequency intraluminal ultrasound study. World J Clin Cases 2021; 9(34): 10566-10575

URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10566.htm

DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10566

### INTRODUCTION

Endoscopic variceal ligation (EVL) was introduced in the 1980s as an alternative to endoscopic injection sclerotherapy[1]. Several prospective trials reported that EVL was superior to endoscopic injection sclerotherapy in that it eradicated varices more rapidly with less recurrent bleeding and fewer complications[2–7]. Thus, EVL has become the endoscopic treatment of choice for both the control of acute bleeding and the prevention of rebleeding from esophageal varices (EV)[8].

Gastric varices (GVs) are commonly categorized based on their location in the stomach and their relationship with EVs[9,10]. Type 1 gastric varices (GOV1) are the most common subtype of GV and constitute an extension of EV along the lesser curvature of the stomach[9,11]. Because they are considered a continuation of EV, current recommendations have emphasized that GOV1 should be treated as EV. In contrast, the other subtypes of GV, such as IGV1 (varices in the gastric fundus), IGV2 (ectopic varices around the pylorus), and GOV2 (varices extending along the greater curvature toward the gastroduodenal junction), do not respond well to therapeutic modalities used for EV[11–13].

After successful control of acute bleeding with emergency EVL, endoscopic follow-up should be repeated, and residual or recurrent varices should be treated with elective EVL to prevent variceal rebleeding if indicated[12,13]. Esophagogastroduodenoscopy (EGD) is the best practical modality for the follow-up of EV after EVL[12]. However, little is known about whether it is an effective modality for post-EVL endoscopic follow-up of GOV1.

Recently, endoscopic ultrasound (EUS) has been introduced as an important modality in the diagnosis of varices[15,16]. In particular, high-frequency intraluminal ultrasound (HFIUS) has been reported to enable quantitative measurement of variceal
size, so it may be a more sensitive and reproducible imaging modality than EGD for the detection of varices and the estimation of their size. However, these data are very limited.

The aims of this study were to examine the diagnostic correlation of EGD grades and HFIUS measurements in estimating post-EVL GOV1 and to evaluate their ability to predict variceal rebleeding based on EGD findings and the cross-sectional area (CSA) of varices using HFIUS.

**MATERIALS AND METHODS**

**Study protocol**
This study was performed at the Konkuk University Medical Center, Seoul, Korea from January 2017 to December 2018. Of the participants with liver cirrhosis with GOV1, consecutive patients who underwent EVL for GOV1 bleeding were initially selected. Patients with hepatocellular carcinoma or Child-Pugh classification C cirrhosis (Child-Pugh class score ≥ 10) were excluded. Within 2 mo after the initial EVL, a follow-up EGD was performed biweekly to reassess variceal grade, and elective EVL was performed to obliterate the residual varices. One to two months after the initial EVL, endoscopic follow-up using synchronous EGD and HFIUS was conducted on 26 patients who were enrolled in this study. Of these, 17 patients whose varices were reduced to grade 0/1 according to EGD were prospectively followed up for 1 year without additional sessions of EVL. Patients received propranolol during follow-up if red color signs (RC signs) were evident on varices and nonselective beta blockers were not contraindicated. Variceal rebleeding was defined as the presence of hematemesis, hematochezia, or melena when the source of the bleeding was endoscopically proven to be GOV1 (spurting or oozing from varices or the presence of a recent blood clot over varices). The primary end point of the study was the correlation between EGD grades and HFIUS measurements as measured by the Spearman correlation coefficient in 26 patients initially enrolled. The secondary end point was the predictabilities for variceal rebleeding of EGD grades and HFIUS measurements in 17 patients who completed the 1-year follow-up. This study was approved by the Institutional Review Board of Konkuk University Hospital and was performed in accordance with the most recent (2008) revision of the Helsinki Declaration, and informed consent was obtained directly from all enrolled patients.

**Diagnostic and therapeutic endoscopy**
EVL was performed using a pneumatic-active ligating device (Samjin, Seoul, Korea) with a 25-cm overtube or using a multiband ligator (Saeed Six Shooter; Cook Endoscopy, Winston-Salem, NC, United States). The variceal hemorrhage site was first ligated. Then, surrounding varices were ligated as much as possible. Concomitant EVs were also ligated.

Follow-up EGD was performed using a double-channel endoscope (GIF2T–240; Olympus Co. Ltd, Tokyo, Japan). During the procedure, endoscopic images were electronically recorded for subsequent review by two endoscopists (JHK and WHC). Post-EVL EGD grades of varices were classified according to the General Rules for Recording Endoscopic Findings of Esophagogastric Varices of the Japanese Research Society for Portal Hypertension: Grade 0, not visible; grade 1, small, straight; grade 2, enlarged, tortuous; grade 3, large, coil-shaped, or tumorous. RC signs were classed as positive or negative. Positive was defined as clear evidence of a cherry-red spot, a red wale marking, or a hemocystic spot.

**HFIUS examination**
HFIUS was performed simultaneously with EGD. The HFIUS catheter assembly consisted of a 2.3-mm diameter ultrasonic miniprobe equipped with a 20-MHz transducer (UM–G20–29R, Olympus). The catheter was inserted via one of the accessory channels, and an automatic water infusion pump was attached to another channel to facilitate infusion of deaerated water. The HFIUS miniprobe, which has an axial resolution of approximately 0.1 mm and a penetration depth of 2.0 cm, was advanced to the mid-body of the stomach and was gradually withdrawn along the lesser curvature until the distal third of the esophagus was scanned. EUS images were recorded electronically for subsequent review by two examiners (JHK and WHC). The largest CSA sizes of varices using HFIUS were estimated using ImageJ software (NIH, Bethesda, MD, United States). The CSA of each varix was measured between the hypoechoic blood-filled lumen and the hyperechoic submucosa or mucosa (Figures 1
Figure 1 High-frequency intraluminal ultrasound images of post-endoscopic variceal ligation of type 1 gastric varices. The post-endoscopic variceal ligation sizes of varices were assessed according to the largest cross-sectional area (CSA). CSA was measured between the hypoechoic blood-filled lumen and the hyperechoic submucosa or mucosa. The dotted line indicates the largest CSA of the varix. The scale bar represents 10 mm.

Statistical analysis
Quantitative variables are expressed as the mean ± SD and were compared using Student’s t test. Qualitative variables were compared using the χ² test. The correlation between EGD grade and HFIUS estimates was analyzed using the Spearman correlation coefficient. Receiver operating characteristic curves and sensitivity and specificity plots were constructed to identify predictors of variceal rebleeding. Cutoff values that resulted in the best sensitivity and specificity were identified. All P values were two-tailed, and a P value < 0.05 was considered significant.

RESULTS
Twenty-six patients were enrolled in this study. Table 1 shows the baseline characteristics of the patients. Varices were reduced to grade 0/1 at EGD findings within four sessions of EVL (single session in 2 patients; two sessions in 5 patients; three sessions in 7 patients; four sessions in 3 patients) in 17 patients, whereas varices were not reduced to grade 0/1 in 9 patients. Among the 17 patients who completed the 1-year follow-up, 6 patients (35%) experienced variceal rebleeding during follow-up. Patient characteristics, such as age, sex, etiology of cirrhosis, and Child-Pugh score, were not significantly associated with variceal rebleeding (Table 2).

In 26 patients, EGD identified GOV1 grades 0, 1, 2, and 3 in 11, 6, 6, and 3 patients, respectively. The mean largest variceal CSA values measured using HFIUS in patients with EGD grades 0, 1, 2, and 3 were 13.9 ± 9.5 mm², 17.2 ± 11.6 mm², 21.0 ± 9.8 mm², and 28.9 ± 18.7 mm², respectively. GOV1 grades estimated using EGD were not significantly correlated with largest variceal CSA measured using EUS (correlation coefficient = 0.36, P = 0.07), and the mean largest variceal CSA of grade 2/3 GOV1 was not significantly different from that of grade 0/1 GOV1 (23.7 ± 12.7 vs 15.1 ± 10.0; P = 0.07) (Figure 3).

Among the 17 patients who completed the 1-year follow-up, the mean largest variceal CSA of GOV1 was significantly greater in patients who experienced rebleeding compared with patients who did not (22.2 ± 7.7 mm² vs 11.2 ± 9.2 mm², respectively; P = 0.03) (Figure 4). A cutoff value of 17.2 mm² for largest variceal CSA resulted in a sensitivity and specificity for subsequent GOV1 bleeding of 83% and 82%, respectively. Rebleeding was significantly more frequent in those with largest variceal CSAs greater than the CSA cutoff value compared with those with largest variceal CSAs less than the CSA cutoff value, whereas EGD grading and RC sign were not predictive of GOV1 rebleeding (Table 3).

DISCUSSION
In this study, we initially enrolled 26 patients with liver cirrhosis with GOV1 who underwent synchronous EGD and HFIUS as endoscopic follow-up after the initial EVL.
Table 1 Baseline characteristics of patients (n = 26) initially enrolled

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52.7 ± 10.5</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>22/4</td>
</tr>
<tr>
<td>Alcohol/nonalcoholic</td>
<td>6/20</td>
</tr>
<tr>
<td>Child-Pugh score 5/6/7/8/9</td>
<td>3/3/8/7/5</td>
</tr>
<tr>
<td>MELD score</td>
<td>12.8 ± 3.8</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Serum albumin (gm/dL)</td>
<td>3.2 ± 0.5</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>2.2 ± 1.3</td>
</tr>
<tr>
<td>Prothrombin time (INR)</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Presence of ascites</td>
<td>12 (46.2%)</td>
</tr>
<tr>
<td>Presence of hepatic encephalopathy</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Platelet count (K/mm$^3$)</td>
<td>88.1 ± 39.8</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>7.8 ± 2.2</td>
</tr>
<tr>
<td>Blood transfused (units)</td>
<td>3.0 ± 1.5</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD. M: Male; F: Female; MELD: Model for end-stage liver disease; INR: International normalized ratio.

Table 2 Predictable factors of rebleeding in patients (n = 17) at the 1-yr follow-up

<table>
<thead>
<tr>
<th></th>
<th>Rebleeding (+)</th>
<th>Rebleeding (-)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55.5 ± 11.8</td>
<td>51.9 ± 10.7</td>
<td>0.533</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>5/9</td>
<td>1/2</td>
<td>0.728</td>
</tr>
<tr>
<td>Alcohol/ nonalcoholic</td>
<td>2/2</td>
<td>4/9</td>
<td>0.445</td>
</tr>
<tr>
<td>Child-Pugh classification A/B</td>
<td>1/3</td>
<td>5/8</td>
<td>0.555</td>
</tr>
<tr>
<td>MELD score</td>
<td>12.8 ± 2.6</td>
<td>13.4 ± 3.1</td>
<td>0.725</td>
</tr>
</tbody>
</table>

M: Male; F: Female; MELD: Model for end-stage liver disease.

and evaluated the diagnostic correlation of these two modalities. Then, in 17 patients with 1-year follow-up, we confirmed that HFIUS was a good predictor of subsequent rebleeding compared with EGD grading.

Theoretically, both GOV1 and EV bleeding can be treated with EVL given their similar pathophysiology\[12\]. Technically as well as theoretically, EVL exhibits an advantage with respect to controlling acute bleeding from GOV1 given its better endoscopic view and easier accessibility compared with other subtypes of GV. However, from a practical perspective, EVL does not always eradicate GOV1 because its effect is limited to superficial layers, and GV often extends into the submucosa or deeper layers\[25,26\]. Therefore, endoscopic follow-ups are very important for preventing GOV1 rebleeding.

EGD is less sensitive than EUS for the evaluation of GV\[22,27–29\]. However, the availability of EUS is limited in clinical practice, and conventional EGD is typically used as an endoscopic follow-up modality after gastric variceal ligation\[24,25\]. It has not been established whether EUS or EGD is more appropriate for post-EVL follow-up of GOV1. In patients with GOV1 in this study, EGD grading was not significantly correlated with post-EVL HFIUS size estimation of GOV1. Moreover, EGD findings, including grading and RC signs, did not predict post-EVL GOV1 bleeding. In contrast, HFIUS measurement of a cutoff value for the largest CSA enabled prediction of rebleeding. Therefore, we suggest that EGD grading is insufficient for post-EVL
<table>
<thead>
<tr>
<th>Endoscopic modality</th>
<th>GOV1, n = 17 (100%)</th>
<th>Rebleeding (+), n = 6 (35%)</th>
<th>Rebleeding (--), n = 11 (65%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFIUS</td>
<td>≥ CSA cutoff value$^1$</td>
<td>5 (29)</td>
<td>2 (12)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>&lt; CSA cutoff value$^2$</td>
<td>1 (6)</td>
<td>9 (53)</td>
<td></td>
</tr>
<tr>
<td>EGD</td>
<td>Grade 1 with RCS</td>
<td>2 (12)</td>
<td>2 (12)</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>Grade 0 or 1 without RCS</td>
<td>4 (24)</td>
<td>9 (53)</td>
<td></td>
</tr>
</tbody>
</table>

$^1$The cutoff value for the largest cross-sectional area was 17.2 mm$^2$. With these cutoff values, the sensitivity and specificity were 83% and 82%, respectively, for post-endoscopic variceal ligation type 1 gastric varices bleeding. The receiver operating characteristic curve had an area below the curve of 0.83 ± 0.10, which was statistically significant (P = 0.03).

CSA: Cross-sectional area; EGD: Esophagogastroduodenoscopy; GOV1: Type 1 gastric varices; HFIUS: High-frequency intraluminal ultrasound; Red color signs.

Figure 2 Representative esophagogastroduodenoscopy and high-frequency intraluminal ultrasound images of type 1 gastric varices. The type 1 gastric varices was grade 0 according to esophagogastroduodenoscopy, but the largest variceal cross-sectional area was 31.4 mm$^2$ according to high-frequency intraluminal ultrasound.

CONCLUSION

To our knowledge, this is the first study in which HFIUS has been used to predict post-EVL GOV1. This study demonstrated that HFIUS measurement is predictive of
Figure 3 Post-endoscopic variceal ligation esophagogastroduodenoscopy grades and cross-sectional areas. The mean largest variceal cross-sectional area (CSA) for grade 0/1 type 1 gastric varices (GOV1) did not differ from that for grade 2/3 GOV1 (15.1 ± 10.0 mm² vs 23.7 ± 12.7 mm², respectively; \( P = 0.07 \)). EUS: Endoscopic ultrasound; EGD: Esophagogastroduodenoscopy.

Figure 4 Comparison of high-frequency intraluminal ultrasound estimates of largest variceal cross-sectional area between patients with or without post-endoscopic variceal ligation variceal bleeding. The mean largest variceal cross-sectional area (CSA) of type 1 gastric varices patients who experienced post-endoscopic variceal ligation (EVL) bleeding was significantly greater than that of patients who did not experience post-EVL bleeding (22.2 ± 7.7 mm² vs 11.2 ± 9.2 mm², respectively; \( P = 0.03 \)). Horizontal bars represent median values, and the upper and lower ends of the bars represent quartile values. EUS: Endoscopic ultrasound.

Post-EVL GOV1 rebleeding; on the other hand, EGD is insufficient. Therefore, we suggest that HFIUS could be mandatory for endoscopic follow-up of GOV1 after EVL.
ARTICLE HIGHLIGHTS

Research background
After successful control of acute bleeding with emergency endoscopic variceal ligation (EVL), endoscopic follow-up should be repeated, and residual or recurrent varices should be treated with elective EVL to prevent variceal rebleeding if indicated. Recently, endoscopic ultrasound (EUS) has been introduced as an important modality in the diagnosis of varices, because EUS is more sensitive than esophagogastroduodenoscopy (EGD) for the evaluation of gastric varices.

Research motivation
The efficacy of endoscopic ultrasonography for the follow-up of gastric varices treated with EVL has not been established.

Research objectives
This study aimed to evaluate the diagnostic correlation of EGD and high-frequency intraluminal ultrasound (HFIUS) for type 1 gastric varices (GOV1) after EVL and to identify the predictability for rebleeding with EGD and HFIUS.

Research methods
In liver cirrhosis patients with GOV1, we performed endoscopic follow-up using EGD and HFIUS synchronously after EVL for hemorrhage from GOV1. Endoscopic grading and red color signs were analyzed using EGD, and the largest variceal cross-sectional areas (CSAs) were measured using HFIUS. In addition, 1-year follow-up was performed. Variceal rebleeding was defined as the presence of hematemesis, hematochezia or melena without other evidence of bleeding on endoscopic follow-up.

Research results
In 26 patients with GOV1, variceal CSA on HFIUS of GOV1 was poorly correlated with EGD grading of GOV1 ($r = 0.36)$. In 17 patients who completed the 1-year follow-up, variceal CSA on HFIUS was a good predictor of subsequent rebleeding, whereas EGD grading was not a predictor of subsequent rebleeding.

Research conclusions
HFIUS measurement is more predictive of GOV1 rebleeding than EGD grading, so HFIUS measurement may be necessary for endoscopic follow-up after EVL in patients with GOV1.

Research perspectives
Future work and basic research should be performed to confirm that EUS, especially HFIUS, could be performed to estimate the accurate variceal size and predict rebleeding of GOV1.

REFERENCES
6 Hou MC, Lin HC, Kuo BI, Chen CH, Lee FY, Lee SD. Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal variceal hemorrhage: a prospective


24 European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompenated cirrhosis. *J Hepatol* 2018; 69: 406-460 [PMID: 29653743 DOI: 10.1016/j.jhep.2018.03.024]


Observational Study

Effects of WeChat platform-based health management on health and self-management effectiveness of patients with severe chronic heart failure

Zhan-Ru Wang, Jia-Wu Zhou, Xiao-Ping Liu, Guo-Juan Cai, Qi-Hong Zhang, Jun-Fang Mao

ORCID number: Zhan-Ru Wang 0000-0002-0655-2493; Jia-Wu Zhou 0000-0002-3680-5914; Xiao-Ping Liu 0000-0002-2155-6716; Guo-Juan Cai 0000-0002-1815-0088; Qi-Hong Zhang 0000-0002-8355-4863; Jun-Fang Mao 0000-0002-3930-7966.

Author contributions: Wang ZR and Zhou JW designed the study; Liu XP drafted the work; Cai GJ and Zhang QH collected the data; Mao JF and Wang ZR analyzed and interpreted the data; Wang ZR, Zhou JW, and Mao JF wrote the article.

Institutional review board statement: This study was approved by the Shaoxing Hospital of China Medical University Ethics Committee.

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 that there is no conflict of interest to disclose.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

Zhan-Ru Wang, Department of Critical Care Medicine, Shaoxing Hospital of China Medical University, Shaoxing 312000, Zhejiang Province, China

Jia-Wu Zhou, Xiao-Ping Liu, Department of Emergency Medicine, Shaoxing Hospital of China Medical University, Shaoxing 312000, Zhejiang Province, China

Guo-Juan Cai, Qi-Hong Zhang, Jun-Fang Mao, Department of Emergency Medicine, Zhuji People’s Hospital of Zhejiang Province, Zhuji 311800, Zhejiang Province, China

Corresponding author: Jun-Fang Mao, MD, Chief Nurse, Department of Emergency Medicine, Zhuji People’s Hospital of Zhejiang Province, No. 9 Jianmin Road, Zhuji 311800, Zhejiang Province, China. maojunfang2021@163.com

Abstract

BACKGROUND
Epidemiological studies have found that the prevalence of chronic heart failure in China is 0.9%, the number of people affected is more than 4 million, and the 5-year survival rate is even lower than that of malignant tumors.

AIM
To determine the impact of WeChat platform-based health management on severe chronic heart failure patients’ health and self-management efficacy.

METHODS
A total of 120 patients suffering from chronic heart failure with cardiac function grade III-IV, under the classification of the New York Heart Association, were admitted to our hospital in May 2017. In January 2020, they were divided into two groups: A control group (with routine nursing intervention) and an observation group (with WeChat platform-based health management intervention). Changes in cardiac function, 6-min walking distance (6MWD), high-sensitivity cardiac troponin (hs-cTnT), and N-terminal pro B-type natriuretic peptide (NT-proBNP) were detected in both groups. The Self-Care Ability Scale (ESCA) score, Minnesota Living with Heart Failure Questionnaire score, and compliance score were used to evaluate self-management ability, quality of life, and compliance of the two groups. During a follow-up period of 12 mo, the occurrence of cardiovascular adverse events in both the groups was counted.
INTRODUCTION

Chronic heart failure is the final stage of various cardiovascular diseases. It is complex and involves multiple complications, a high case fatality rate, and a profoundly negative prognosis. Patients frequently need to be hospitalized, which may not only lead to deterioration of their condition, but also add an economic burden on them, causing medical resource waste. Therefore, maintaining a stable condition of chronic heart failure has become a key objective in clinical treatments[1]. However, the phenomena of worsening cardiac situations and repeated hospitalizations are currently very common given that there are no effective approaches to address the issues of health intervention subsequent to the discharge of patients and their poor self-management capabilities. Under the present conventional nursing model, interventions for patients outside the hospital consist of discharge guidance and self-management capabilities. Under the present conventional nursing model, the control group before intervention, and the LiHFe scores of the observation group were lower than those of the control group (< 0.05). The Minnesota heart failure quality of life (LiHFe) scores of physical restriction, disease symptoms, psychological emotion, social relations, and other items were decreased compared to those of the control group before intervention, and the LiHFe scores of the observation group were significantly improved compared to those of the control group (P < 0.05). With intervention, the compliance scores of rational diet, regular medication, healthy behavior, and timely reexamination were increased, thereby leading to the compliance scores of the observation group being significantly improved compared to those of the control group (P < 0.05). During the 12 mo follow-up, the incidence rates of acute myocardial infarction and cardiogenic rehospitalization in the observation group were lower than those of the control group, and the hospitalization time in the observation group was shorter than that of the control group, but there was no significant difference between the two groups (P > 0.05).

CONCLUSION

WeChat platform-based health management can improve the self-care ability and compliance of patients with severe chronic heart failure, improve the cardiac function and related indexes, reduce the occurrence of cardiovascular adverse events, and enable the avoidance of rehospitalization.

Key Words: WeChat platform; Health management; Severe chronic heart failure; Self-care capacity; Cardiac function; Adverse cardiovascular events

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Through a set of retrospective studies, it was confirmed that health management based on the WeChat platform can improve the self-care ability and compliance of patients with severe chronic heart failure, improve the cardiac function and related indexes, reduce the occurrence of cardiovascular adverse events, and avoid rehospitalization.

Citation: Wang ZR, Zhou JW, Liu XP, Cai GJ, Zhang QH, Mao JF. Effects of WeChat platform-based health management on health and self-management effectiveness of patients with severe chronic heart failure. World J Clin Cases 2021; 9(34): 10576-10584
URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10576.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10576
telephonic interviews, and their impacts are barely satisfactory[2].

Continuing nursing care is an emerging nursing model that is an extension of hospital care. It ensures that patients receive sustained and efficient care interventions and are able to solve health problems when they are discharged[3]. WeChat is a common and good real-time social application with high interactivity and is utilized frequently in the medical field[4]. In this study, we applied WeChat to continue nursing care outside the hospital for severe patients with chronic heart failure and observed the impact of the WeChat platform-based health management approach on the health of the patients and the efficiency of self-management.

MATERIALS AND METHODS

General information
One hundred and twenty patients with chronic heart failure with cardiac function of grade III-IV, under the New York Heart Association (NYHA), were admitted to our hospital in May 2017. In January 2020, they were divided into two groups: A control group (with routine nursing intervention) and an observation group (with WeChat platform-based health management intervention). The inclusion criteria for the patients were as follows: (1) Suiting the standard of chronic heart failure provided in the Chinese Guidelines for the Diagnosis and Treatment of Heart Failure; (2) being in the age group of 18-75 years; (3) having NYHA grade III-IV cardiac function; (4) having a good mastery over using WeChat and residing locally; (5) having an expected lifetime of 12 mo or more; and (6) providing their informed consent. The exclusion criteria were as follows: (1) Having an abnormal function of limbs; (2) suffering from valvular heart disease and/or Cor pulmonale; (3) being diagnosed as insane; (4) having severe infections; and (5) having uncontrollable diseases such as hypertension and diabetes.

There were 60 cases in the control group, with 36 patients being male and 24 being female. The age range was 40 years to 75 years and the average age (mean ± SD) was 58.69 ± 10.13 years. There were 60 cases in the observation group, with 32 patients being male and 24 being female. The age range was 40 years to 75 years and the average age was 59.41 ± 11.05 years.

Methods
The control group received conventional care intervention and discharge guidance, including reasonable diet, usage of drugs under instruction, proper exercise, and an appointment for the next visit to the hospital. Telephonic follow-ups were done regularly when they were discharged from the hospital.

The observation group received WeChat platform-based health management intervention. The WeChat health management group was composed of a doctor, a nurse, and an administrator on the network platform. The administrator built the group and the official accounts of health management, and ensured that both were maintained and run routinely. Medical staff regularly published relevant knowledge about self-management of chronic heart failure, including basic knowledge of cardiovascular diseases, a regular schedule to adhere to, diet and drug instructions, sports guidance, emotion management, etc. This content was issued in the form of pictures, texts, audio notes, and video notes, once a day. WeChat provided personalized instructions, propagated health behavior interventions, and instructed patients, whose conditions were getting worse, to obtain medical treatment instantly, and also assisted them with arranging hospitalization via private talks.

Measurements
The cardiac function indexes, left ventricular ejection fraction (LVEF) and stroke output (SV), were detected using an ultrasonic cardiogram before and after the 12-mo interventions. The detection equipment used was a Philips IE33 Color Doppler Ultrasound diagnostic instrument with a probe frequency of 3.0-7.5 MHz. Fasting venous blood (3 mL) was collected from the patients, and centrifuged for 10 min at 3500 r/min within 1 h after the blood collection. The serum was tested for high-sensitivity cardiac troponin (hs-cTnT) and N-terminal pro B-type natriuretic peptide (NT-proBNP) by enzyme-linked immunosorbent assay. The kit was manufactured by Shanghai Enzyme Link Biotechnology Co., Ltd., and the instrument used was the RT-96A enzyme label instrument manufactured by Shenzhen Mindray Medical Electronics Co., Ltd.
Evaluation standards
The Self-care Ability Scale (ESCA) score, Minnesota heart failure quality of life (LiHFe) score, and compliance score were used to evaluate the self-management ability, quality of life, and compliance of both groups.

The ESCA score includes 43 items of self-care responsibility, self-concept, self-care skills, and self-care health knowledge, and the score is positively correlated with self-management ability. The LiHFe score includes 21 items in total, including physical limitations, disease symptoms, psychological emotions, and social relationships. A 6-segment scoring method is applied, and the score is inversely proportional to the quality of life[5]. The compliance score includes a reasonable diet, regular medication, healthy behavior, and timely review. This scale is a self-designed score by the hospital, with a single score ranging from 0 to 10 points, which is proportionate to compliance by the patient.

Follow-up information
The occurrence and hospitalization time of cardiovascular adverse events (i.e., aggravation of heart failure, acute myocardial infarction, severe arrhythmia, cardiogenic readmission, etc.) in both groups were recorded by the outpatient service or WeChat platform for 12 mo.

Statistical analysis
Statistical analyses were performed with SPSS19.0. Measuring index are expressed as the mean ± SD and were compared by the t test. Count data were compared by the χ² test. Statistical significance was defined as P < 0.05.

RESULTS

Comparison of baseline data between the two groups
There was no statistical significance when comparing the baseline data between the two groups (P > 0.05; Table 1).

Comparison of heart function between the two groups
The LVEF and SV rose after intervention in both groups. Further, the heart function after intervention of the observation group significantly increased compared to that of the control group (P < 0.05; Table 2).

Comparison of 6-min walking distance, hs-cTnT, and NT-proBNP between the two groups
After intervention, the 6-min walking distance (6 MWD) increased, and the hs-cTnT and NT-proBNP decreased in both groups; the 6MWD, hs-cTnT, and NT-proBNP after intervention of the observation group significantly increased compared to those of the control group (P < 0.05; Table 3).

Comparison of ESCA scores between the two groups
After intervention, ESCA scores of self-care responsibility, self-concept, self-care skills, self-care health knowledge, etc. increased in both groups and ESCA scores after intervention of the observation group significantly increased compared to those of the control group (P < 0.05; Table 4).

Comparison of LiHFe scores between the two groups
After intervention, LiHFe scores of physical limitations, disease symptoms, psychological emotions, social relationships, etc. decreased in both groups and the LiHFe scores after intervention of the observation group significantly increased compared to those of the control group (P < 0.05; Table 5).

Comparison of compliance scores between the two groups
After intervention, compliance scores of reasonable diet, regular medication, healthy behavior, timely review, etc. increased in both groups and compliance scores after intervention in the observation group significantly increased compared to those of the control group (P < 0.05; Table 6).
**Table 1 Comparison of baseline data between the two groups, n (%)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (n = 60)</th>
<th>Observation group (n = 60)</th>
<th>$\chi^2/t$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (75.00)</td>
<td>32 (53.33)</td>
<td>0.543</td>
<td>0.461</td>
</tr>
<tr>
<td>Female</td>
<td>24 (35.00)</td>
<td>28 (46.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.69 ± 10.13</td>
<td>59.41 ± 11.05</td>
<td>0.372</td>
<td>0.711</td>
</tr>
<tr>
<td>Course (yr)</td>
<td>6.36 ± 1.24</td>
<td>6.24 ± 1.57</td>
<td>0.465</td>
<td>0.643</td>
</tr>
<tr>
<td>History of smoking</td>
<td></td>
<td></td>
<td>1.234</td>
<td>0.267</td>
</tr>
<tr>
<td>Yes</td>
<td>22 (36.67)</td>
<td>28 (46.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>38 (63.33)</td>
<td>32 (53.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA classification</td>
<td></td>
<td></td>
<td>0.534</td>
<td>0.465</td>
</tr>
<tr>
<td>III</td>
<td>31 (51.67)</td>
<td>27 (45.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>29 (48.33)</td>
<td>33 (55.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart-based diseases</td>
<td></td>
<td></td>
<td>2.394</td>
<td>0.495</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>5 (8.33)</td>
<td>9 (15.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>10 (16.67)</td>
<td>12 (20.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>18 (30.00)</td>
<td>19 (31.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High blood pressure</td>
<td>27 (45.00)</td>
<td>20 (33.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>15 (25.00)</td>
<td>21 (35.00)</td>
<td>1.429</td>
<td>0.232</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (50.00)</td>
<td>33 (55.00)</td>
<td>0.301</td>
<td>0.583</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (31.67)</td>
<td>15 (25.00)</td>
<td>0.657</td>
<td>0.418</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td>1.295</td>
<td>0.523</td>
</tr>
<tr>
<td>Junior high school and below</td>
<td>12 (20.00)</td>
<td>9 (15.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary and tertiary</td>
<td>24 (40.00)</td>
<td>21 (35.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undergraduate and above</td>
<td>24 (40.00)</td>
<td>30 (50.00)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2 Comparison of heart function between the two groups (mean ± SD)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>LVEF (%)</th>
<th>SV (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-intervention</td>
<td>After intervention</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>34.23 ± 4.26</td>
<td>48.23 ± 4.63*</td>
</tr>
<tr>
<td>Observation</td>
<td>60</td>
<td>33.97 ± 4.51</td>
<td>60.44 ± 4.58*</td>
</tr>
<tr>
<td>t</td>
<td>0.325</td>
<td>14.522</td>
<td>1.191</td>
</tr>
<tr>
<td>P value</td>
<td>0.746</td>
<td>0.000</td>
<td>0.236</td>
</tr>
</tbody>
</table>

*P < 0.05 vs before intervention.
LVEF: Left ventricular ejection fraction; SV: stroke output.

**Comparison of adverse cardiovascular events between the two groups**

During the follow-up period of 12 mo, the observation group had lower acute myocardial infarction incidence and cardiogenic readmission rates, and also had shorter hospital stays compared to the control group. There was no statistical difference in the incidence rates of the aggravation of heart failure and severe arrhythmia between the two groups (P > 0.05; Table 7).
Table 3 Comparison of 6-min walking distance, high-sensitivity cardiac troponin, N-terminal pro B-type natriuretic peptide between the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>6MWD (m)</th>
<th>hs-cTnT (µg/L)</th>
<th>NT-proBNP (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Pre-intervention</strong></td>
<td><strong>After intervention</strong></td>
<td><strong>Pre-intervention</strong></td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>352.69 ± 57.89</td>
<td>468.22 ± 67.41&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.70 ± 0.22</td>
</tr>
<tr>
<td>Observation</td>
<td>60</td>
<td>346.85 ± 62.08</td>
<td>519.36 ± 57.23&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.72 ± 0.21</td>
</tr>
<tr>
<td>t value</td>
<td></td>
<td>0.533</td>
<td>4.480</td>
<td>0.509</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.595</td>
<td>0.000</td>
<td>0.611</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05 vs before intervention.

6MWD: 6-min walking distance; hs-cTnT: High-sensitivity cardiac troponin; NT-proBNP: N-terminal pro B-type natriuretic peptide.

Table 4 Comparison of Self-Care Ability Scale scores between the two groups (mean ± SD, subdivision)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Self-care responsibility</th>
<th>Self-concept</th>
<th>Self-care skills</th>
<th>Self-care health knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Pre-intervention</strong></td>
<td><strong>After intervention</strong></td>
<td><strong>Pre-intervention</strong></td>
<td><strong>After intervention</strong></td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>19.16 ± 2.94</td>
<td>21.13 ± 2.32&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19.85 ± 3.56</td>
<td>22.34 ± 3.69&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Observation</td>
<td>60</td>
<td>18.97 ± 3.02</td>
<td>22.78 ± 3.17&lt;sup&gt;c&lt;/sup&gt;</td>
<td>19.74 ± 3.62</td>
<td>24.87 ± 4.05&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>t value</td>
<td></td>
<td>0.349</td>
<td>3.254</td>
<td>0.168</td>
<td>3.577</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.728</td>
<td>0.001</td>
<td>0.867</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05 vs before intervention.

Table 5 Comparison of Minnesota heart failure quality of life scores between the two groups (mean ± SD, subdivision)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Physical limitations</th>
<th>Symptoms of illness</th>
<th>Psychological mood</th>
<th>Social relations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Pre-intervention</strong></td>
<td><strong>After intervention</strong></td>
<td><strong>Pre-intervention</strong></td>
<td><strong>After intervention</strong></td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>19.24 ± 2.46</td>
<td>15.63 ± 2.01&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13.56 ± 2.12</td>
<td>11.36 ± 1.75&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Observation</td>
<td>60</td>
<td>19.15 ± 2.73</td>
<td>11.67 ± 1.45&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13.61 ± 2.08</td>
<td>10.02 ± 1.51&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>t value</td>
<td></td>
<td>0.190</td>
<td>12.376</td>
<td>0.130</td>
<td>4.491</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.850</td>
<td>0.000</td>
<td>0.896</td>
<td>0.000</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05 vs before intervention.

DISCUSSION

WeChat platform-based health management carries out health education, drug instructions, management of health behaviors etc. by utilizing a social application called WeChat. It belongs to the field of continuing nursing care[6-8]. In recent years, WeChat platform interventions have been applied to various fields, such as chronic diseases, diabetes, coronary heart disease, chronic renal failure, and antenatal guidance[9].

A WeChat platform-based health management style was utilized in cases of severe chronic heart failure in this study, which could promote the capabilities of self-care responsibility, self-conception, self-care skills, self-care health knowledge, etc., as well as moderate life qualities of physical limitations, disease symptoms, psychological emotions, social relationships, etc.; and improve compliance with a reasonable diet, regular medication, healthy behavior, and timely review. This is because official
Table 6 Comparison of compliance scores between the two groups (mean ± SD, subdivision)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Reasonable diet</th>
<th>Regular drug use</th>
<th>Health behaviour</th>
<th>Review on time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-intervention</td>
<td>After intervention</td>
<td>Pre-intervention</td>
<td>After intervention</td>
<td>Pre-intervention</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>5.78 ± 1.32</td>
<td>7.23 ± 1.45</td>
<td>8.24 ± 0.63</td>
<td>5.41 ± 1.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.07 ± 1.39</td>
<td>8.41 ± 0.67</td>
<td>5.32 ± 1.14</td>
<td>7.41 ± 0.82</td>
</tr>
<tr>
<td>Observation</td>
<td>60</td>
<td>5.82 ± 1.07</td>
<td>8.69 ± 1.12</td>
<td>9.32 ± 0.57</td>
<td>8.75 ± 0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.62 ± 1.10</td>
<td>9.23 ± 0.67</td>
<td>5.32 ± 1.05</td>
<td>9.23 ± 0.57</td>
</tr>
<tr>
<td>t</td>
<td>0.182</td>
<td>6.172</td>
<td>0.136</td>
<td>9.026</td>
<td>0.490</td>
</tr>
<tr>
<td>P value</td>
<td>0.856</td>
<td>0.000</td>
<td>0.892</td>
<td>0.000</td>
<td>0.625</td>
</tr>
</tbody>
</table>

*P < 0.05 vs before intervention.

Table 7 Comparison of adverse cardiovascular events between the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Increased heart failure</th>
<th>Acute myocardial infarction</th>
<th>Severe arrhythmia</th>
<th>Cardiogenic rehospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospitalization rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospitalization time</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>5 (8.33)</td>
<td>8 (13.33)</td>
<td>6 (10.00)</td>
<td>17 (28.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.25 ± 4.23</td>
</tr>
<tr>
<td>Observation</td>
<td>60</td>
<td>2 (3.33)</td>
<td>2 (3.33)</td>
<td>3 (5.00)</td>
<td>7 (11.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.36 ± 3.12</td>
</tr>
<tr>
<td>χ²/t</td>
<td>1.365</td>
<td>3.927</td>
<td>1.081</td>
<td></td>
<td>5.208</td>
</tr>
<tr>
<td>P value</td>
<td>0.243</td>
<td>0.048</td>
<td>0.298</td>
<td></td>
<td>0.022</td>
</tr>
</tbody>
</table>

accounts on the WeChat platform regularly published self-management-related intellectual property relating to chronic heart failure to help patients grasp the main points and skills of self-management. They also answered questions online on WeChat group communications to assist patients in mastering the main points of knowledge better through interaction, as well as urge them to engage in health management in order to improve self-care capability and treatment compliance. After building an electronic medical record, we required patients to report their self-measuring indexes every day to give medically accurate information on changes in their disease conditions and enable them to gain personalized intervention through private talks to recognize and deal with risk elements in time, control disease conditions effectively, and improve quality of life.

LVEF and SV are indicators of cardiac pumping function. A decrease in LVEF indicates myocardial contractility weakening[10-13] and the 6MWD reflects the supportive force of cardiopulmonary function for exercise[14]. Hs-cTnT is a structural protein of cardiomyocytes, and its elevation in serum levels indicates myocardial injury and necrosis[15-19]. NT-proBNP is an endogenous hormone secreted by ventricular myocytes, and its serum level reflects the degree of myocardial damage, which is an important index for clinical evaluation of the degree of heart failure[20]. This study used indexes of ultrasound cardiograms and laboratory serum to estimate the condition of patients. The 6MWD was used to appraise exercise tolerance. We found that a health management style based on the WeChat platform in cases of severe chronic heart failure can promote the expression of heart function and related indicators, which favor disease control. During the 12-mo follow-up, we found that the WeChat platform-based health management style, in cases of severe chronic heart failure, reduced the acute myocardial infarction incidence and cardiogenic readmission rates and shortened hospital stays. Patients experienced the favorable effects of intervention in many aspects, such as healthy lifestyle, objecting to medical advice, and controlling their diseases during the interventions out of the hospital, by improved compliance with a reasonable diet, regular medication, healthy behavior, timely review, etc. In daily reports, in every self-measuring index, the medical staff and patient were able to easily note changes in disease condition in time, make relative adjustments in treatment, and prevent deterioration and relapse of the condition, which will ultimately have a better curative effect in the long term.
CONCLUSION

In summary, WeChat platform-based health management can improve the self-care ability and compliance of patients with severe chronic heart failure, improve the cardiac function and related indexes, reduce the occurrence of cardiovascular adverse events, and avoid rehospitalization.

ARTICLE HIGHLIGHTS

Research background
The prevalence of chronic heart failure in China continues to rise. Continuing nursing care is an emerging nursing model that is an extension of hospital care. WeChat is a common and good real-time social application with high interactivity and is utilized frequently in the medical field.

Research motivation
This study explored the impact of WeChat platform-based health management on the treatment of patients with severe chronic heart failure.

Research objectives
The study aimed to explore the significance of health management based on WeChat platform in the treatment of patients with severe chronic heart failure.

Research methods
In May 2017, a group study of 120 patients with chronic heart failure grade III-IV heart function classified by the New York Heart Association was conducted at our hospital.

Research results
The left ventricular ejection fraction, stroke output, and 6-min walking distance (6MWD) increased, and the high-sensitivity cardiac troponin (hs-cTnT) and N-terminal pro B-type natriuretic peptide (NT-proBNP) decreased in both groups, as compared to those before the intervention. Further, cardiac function during the 6MWD, hs-cTnT, and NT-proBNP improved significantly in the observation group after intervention ($P < 0.05$).

Research conclusions
Health management based on the WeChat platform can improve the self-care ability and compliance of patients with severe chronic heart failure, reduce the occurrence of adverse cardiovascular events, and avoid rehospitalization.

Research perspectives
Health management based on the WeChat platform can play a greater role in the treatment of cardiovascular diseases.

REFERENCES


5. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure


Observational Study

Early cardiopulmonary resuscitation on serum levels of myeloperoxidase, soluble ST2, and hypersensitive C-reactive protein in acute myocardial infarction patients

Min Hou, Ya-Ping Ren, Rui Wang, Lin-Xin Lu

ORCID number: Min Hou 0000-0002-6848-6452; Ya-Ping Ren 0000-0002-7854-2104; Rui Wang 0000-0002-1199-814X; Lin-Xin Lu 0000-0001-8645-1256.

Author contributions: Hou M and Lu LX analyzed the data and drafted the paper; Wang R revised the chart of the paper; Ren YP and Hou M analyzed the data and revised and finalized the manuscript for publication.

Institutional review board statement: The study was reviewed and approved by the Bethune Hospital in Shanxi Institutional Review Board.

Informed consent statement: All study participants provided informed written consent.

Conflict-of-interest statement: None conflict of interest.

Data sharing statement: No additional data are available.

Supported by Key R&D Projects in Shanxi Province, China, No. 201903D321184.

Country/Territory of origin: China

Specialty type: Emergency Medicine

Min Hou, Rui Wang, Lin-Xin Lu, Department of Emergency, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan 030032, Shanxi Province, China

Min Hou, Ya-Ping Ren, Rui Wang, Lin-Xin Lu, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China

Ya-Ping Ren, Department of Cardiology, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan 030032, Shanxi Province, China

Corresponding author: Lin-Xin Lu, BM BCh, Chief Physician, Department of Emergency, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, No. 99 Longcheng Street, Xiaodian District, Taiyuan 030001, Shanxi Province, China. llx6477@163.com

Abstract

BACKGROUND
Prompt and effective cardiopulmonary resuscitation (CPR) can promote the recovery of spontaneous circulation to some extent and can save patients’ lives. The minimum target of cardiac resuscitation is the restoration of spontaneous circulation (ROSC). However, owing to prolonged sudden cardiac arrest, there is relatively high mortality within 24 h after cardiac resuscitation. Moreover, severe cerebral anoxia can deteriorate the prognosis of patients. Therefore, it is important to adopt an effective clinical evaluation of acute myocardial infarct (AMI) patients’ prognosis after cardiac resuscitation for the purpose of prevention and management.

AIM
To investigate early CPR effects on human myeloperoxidase (MPO), soluble ST2 (sST2), and hypersensitive C-reactive protein (hs-CRP) levels in AMI patients.

METHODS
In total, 54 patients with cardiac arrest caused by AMI in our hospital were selected as the observation group, and 50 other patients with AMI were selected as the control group. The differences in serum levels of MPO, sST2, and hs-CRP...
Hou M et al. Early cardiopulmonary resuscitation in AMI

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Received: July 23, 2021
Peer-review started: July 23, 2021
First decision: August 19, 2021
Revised: August 22, 2021
Accepted: October 14, 2021
Article in press: October 14, 2021
Published online: December 6, 2021

P-Reviewer: Reyher C
S-Editor: Wang JL
L-Editor: Filipodia
P-Editor: Wang JL

between the observation group and the control group were tested, and the differences in the serum levels of MPO, sST2, and hs-CRP in ROSC and non-ROSC patients, and in patients who died and in those who survived, were analyzed.

RESULTS
Serum levels of MPO, sST2, hs-CRP, lactic acid, creatine kinase isoenzyme (CK-MB), and cardiac troponin I (cTnI) were significantly higher in the observation group than in the control group (P < 0.05). Serum levels of MPO, sST2, hs-CRP, lactic acid, CK-MB, and cTnI in the observation group were lower after CPR than before CPR (P < 0.05). In the observation group, MPO, sST2, hs-CRP, lactic acid, CK-MB, and cTnI serum levels were lower in ROSC patients than in non-ROSC patients (P < 0.05). MPO, sST2, hs-CRP, and lactic acid serum levels of patients who died in the observation group were higher than those of patients who survived (P < 0.05). The areas under receiver operating characteristic curve predicted by MPO, sST2, hs-CRP, lactic acid, CK-MB, and cTnI were 0.616, 0.681, 0.705, 0.704, 0.702, and 0.656, respectively (P < 0.05). The areas under receiver operating characteristic curve for MPO, sST2, hs-CRP, and lactic acid to predict death were 0.724, 0.800, 0.689, and 0.691, respectively (P < 0.05). Logistic regression analysis showed that MPO, sST2, and hs-CRP were the influencing factors of ROSC (odds ratios = 1.667, 1.589, and 1.409, P < 0.05), while MPO, sST2, hs-CRP, and lactic acid were the influencing factors of death (odds ratios = 1.624, 1.525, 1.451, and 1.365, P < 0.05).

CONCLUSION
Serum levels of MPO, sST2, hs-CRP, and lactic acid have a certain value in predicting recovery and prognosis of patients with ROSC.

Key Words: Acute myocardial infarction; Cardiac arrest; Human myeloperoxidase; Soluble ST2; Hypersensitive C-reactive protein; Lactic acid

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Acute myocardial infarction (AMI) is one of the leading causes of death. Novel cardiac markers have provided an effective method for early diagnosis of AMI. Our study mainly explored and discussed the effects of early cardiopulmonary resuscitation on serum levels in AMI patients.

Citation: Hou M, Ren YP, Wang R, Lu LX. Early cardiopulmonary resuscitation on serum levels of myeloperoxidase, soluble ST2, and hypersensitive C-reactive protein in acute myocardial infarction patients. World J Clin Cases 2021; 9(34): 10585-10594

URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10585.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10585

INTRODUCTION
Acute myocardial infarction (AMI) is one of the leading causes of death. Therefore, early detection, diagnosis, and treatment are of great significance[1]. The traditional diagnosis of AMI mainly relies on examining myocardial enzyme profiles. However, elevation of markers is usually significant 4 h after AMI, which can lead to misdiagnosis and missed diagnosis of AMI[2].

In recent years, novel cardiac markers have provided an effective method for the early diagnosis of AMI[3]. AMI patients receive treatment with percutaneous coronary intervention to dredge the blocked blood vessel, significantly reducing the incidence of adverse cardiac events[4]. However, many patients eventually succumb to adverse cardiac events due to severe systemic or local cardiac inflammation. To cope with immediate cardiac arrest after AMI, timely cardiopulmonary resuscitation (CPR) is the main approach to shorten the duration of myocardial ischemia and hypoxia, thus improving the prognosis of patients[5]. Our study mainly explored and discussed the effects of early cardiopulmonary resuscitation on serum levels of human myeloper-
oxidase (MPO), soluble ST2 (sST2), and hypersensitive C-reactive protein (hs-CRP) in patients with cardiac arrest caused by AMI.

MATERIALS AND METHODS

Baseline data of patients
A total of 54 AMI patients with cardiac arrest who were managed in our hospital from January 2020 to April 2021 were selected as the observation group. The following were the inclusion criteria: (1) diagnosis of AMI based on standards of "Practical Internal Medicine" [6]; (2) meets criteria of cardiac arrest: Loss of consciousness, with or without the disappearance of great artery pulsation, no spontaneous breathing or sighing breathing; (3) time from onset to admission ≤ 6 h; and (4) informed consent obtained from the patient’s family. The following were the exclusion criteria: (1) patients with absolute contraindication to CPR; and (2) those with complications, such as malignancy, liver and kidney dysfunction, and blood system diseases. Fifty patients with AMI were selected as the control group (Table 1).

Empirical method
About 10 mL of venous blood from the patients’ elbow was extracted before and after treatment. A 2500 r/min centrifuge with a centrifugation radius of 6 cm was used for 5 min to separate the supernatant. Double antibody sandwich chemiluminescent immunoassay was used to detect the levels of MPO and cardiac troponin I (cTnI). Biotinylated monoclonal MPO- and cTnI-specific antibodies were mixed with serum to form an antigen-antibody complex. Next, streptomycin magnetic beads were added for incubation. The magnetic beads were adsorbed on the electrode surface by the combination of biotin and streptavidin. Electrode voltage promoted the chemiluminescence of the complex and measured the luminescence intensity. Elecsys software was used to automatically calculate MPO contents and high-sensitive cardiac troponin T through the calibration curve. Serum levels of lactic acid, SST2, and hs-CRP were determined using an enzyme-linked immunosorbent assay kit (Shanghai Enzyme Link Industrial Co., Ltd., Shanghai, China). Biochemical indices included creatine kinase isoenzyme (CK-MB), serum creatinine (Scr), blood urea nitrogen (BUN), and the ratio of aspartate aminotransferase to alanine aminotransferase. The Japan 7170A automatic biochemical analyzer was used to detect cTnI using a rapid test kit.

Treatment method
The medical staff evaluated and examined the patients’ vital indicators at the scene. CPR was initiated if the patient had no vital signs. We made sure the patient was lying flat when chest compressions were performed. The palms of both hands were placed on the xiphoid process of the patient’s chest with appropriate folding methods, and the pressure applied was vertical to the weight and the strength of the body. The depth of the pressure in adult was a sternum depression of > 5 cm, and the pressure was maintained 30 times in each group with the frequency of 100 times per min. The patients’ airways were kept open, their head and neck were lifted, and any dirt in the mouth was removed. Subsequently, they were provided artificial respiration twice. The patients’ nasal cavities were closed when blowing, and the air was made sufficient to make the patients’ chest rise and fall. The ratio of chest compressions to artificial respiration was 30:2. Restoration of spontaneous circulation (ROSC) was achieved if after cardiac arrest, continuous heartbeat, and breathing resumed within 24 h after treatment.

Statistical analysis
SPSS software version 22.0 (Armonk, NY, United States) was used for all statistical analyses. Statistical significance was set at $P < 0.05$. Measurement data conforming to normal distribution were expressed as mean ± SD, and the t-test was used to compare groups. Enumeration data were expressed as frequency or percentage, and comparisons between groups were made using the $\chi^2$ test. The predicted value was analyzed by the receiver operating characteristic (ROC) curve. Logistic regression was used for multivariate analysis.
Table 1 Comparison of baseline data between the observation group and the control group, n (%)

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Observation group (n = 54)</th>
<th>Control group (n = 50)</th>
<th>t or χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / female</td>
<td>32/22</td>
<td>31/19</td>
<td>0.082</td>
<td>0.775</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.60 ± 6.67</td>
<td>57.12 ± 7.10</td>
<td>-0.385</td>
<td>0.701</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.19 ± 2.03</td>
<td>22.03 ± 2.17</td>
<td>0.389</td>
<td>0.698</td>
</tr>
<tr>
<td>Smoking</td>
<td>34 (62.96)</td>
<td>32 (64.00)</td>
<td>0.012</td>
<td>0.913</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (61.11)</td>
<td>29 (58.00)</td>
<td>0.104</td>
<td>0.747</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (29.63)</td>
<td>17 (34.00)</td>
<td>0.229</td>
<td>0.632</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>20 (37.04)</td>
<td>15 (30.00)</td>
<td>0.576</td>
<td>0.448</td>
</tr>
</tbody>
</table>

RESULTS

Comparison of serum indices between the observation and control groups

The serum levels of MPO, sST2, hs-CRP, lactic acid, CK-MB, and cTnI in the observation group were significantly higher than those in the control group (P < 0.05). There was no significant difference in the serum levels of Scr and BUN between the two groups (P > 0.05, Table 2).

Comparison of serum indices in the observation group before and after CPR

The serum levels of MPO, sST2, hs-CRP, lactic acid, CK-MB, and cTnI in the observation group after CPR were significantly lower than those before CPR (P < 0.05) (Table 3).

Comparison of serum indices in the observation group between ROSC and non-ROSC patients

The serum levels of MPO, sST2, hs-CRP, lactic acid, CK-MB, and cTnI in ROSC patients of the observation group were significantly lower than those of non-ROSC patients (P < 0.05) (Table 4).

Comparison of serum indices in the observation group before CPR between patients who died and survived

The serum levels of MPO, sST2, hs-CRP, and lactic acid in patients who died in the observation group before CPR were significantly higher than those of patients who survived (P < 0.05). However, there was no significant difference in the serum levels of CK-MB and cTnI in the observation group between those patients who died and those who survived (P > 0.05) (Table 5).

Value of serum levels of MPO and sST2 in predicting ROSC and death

The areas under the ROC curve predicted by MPO, sST2, hs-CRP, lactic acid, CK-MB, and cTnI were 0.616, 0.681, 0.705, 0.704, 0.702, and 0.656, respectively (P < 0.05), as shown in Figure 1A, while the specific parameters are shown in Table 6. On the other hand, the areas under the ROC curve for MPO, sST2, hs-CRP, and lactic acid in predicting death were 0.724, 0.800, 0.689, and 0.691, respectively (P < 0.05), as shown in Figure 1B, while the specific parameters are shown in Table 7.

Multivariate analysis results

Logistic regression analysis was conducted with MPO, sST2, hs-CRP, lactic acid, CK-MB, and cTnI as independent variables and ROSC (or non-ROSC) as the dependent variable. The results showed that MPO, sST2, and hs-CRP were the influencing factors of ROSC [odds ratios (OR) = 1.667, 1.589, and 1.409, respectively, P < 0.05] (Table 8). Moreover, logistic regression analysis was conducted with MPO, sST2, and hs-CRP as independent variables, and death (or survival) as the dependent variable. The results showed that MPO, sST2, hs-CRP, and lactic acid were the influencing factors for death (OR = 1.624, 1.525, 1.451, and 1.365, respectively, P < 0.05) (Table 9).
Table 2 Comparison of serum indices between the observation group and the control group

<table>
<thead>
<tr>
<th>Index</th>
<th>Control group (n = 54)</th>
<th>Control group (n = 50)</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPO (ng/L)</td>
<td>2.95 ± 0.89</td>
<td>2.01 ± 0.92</td>
<td>5.295</td>
<td>0.000</td>
</tr>
<tr>
<td>sST2 (pg/L)</td>
<td>115.50 ± 21.10</td>
<td>96.60 ± 17.22</td>
<td>4.981</td>
<td>0.000</td>
</tr>
<tr>
<td>hs-CRP (ng/L)</td>
<td>3.76 ± 0.97</td>
<td>2.67 ± 0.87</td>
<td>6.015</td>
<td>0.000</td>
</tr>
<tr>
<td>Lactic acid (mmol/L)</td>
<td>5.77 ± 0.88</td>
<td>5.02 ± 0.92</td>
<td>4.249</td>
<td>0.000</td>
</tr>
<tr>
<td>CK-MB (U/L)</td>
<td>76.39 ± 8.28</td>
<td>65.50 ± 12.21</td>
<td>5.358</td>
<td>0.000</td>
</tr>
<tr>
<td>cTnl (μg/L)</td>
<td>4.59 ± 0.82</td>
<td>3.83 ± 0.90</td>
<td>4.506</td>
<td>0.000</td>
</tr>
<tr>
<td>Scr (μmol/L)</td>
<td>78.29 ± 21.12</td>
<td>74.40 ± 19.18</td>
<td>0.981</td>
<td>0.329</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>6.70 ± 1.00</td>
<td>6.92 ± 1.04</td>
<td>-1.100</td>
<td>0.274</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>32.20 ± 9.29</td>
<td>34.40 ± 8.15</td>
<td>-1.279</td>
<td>0.204</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>29.38 ± 5.60</td>
<td>30.10 ± 5.12</td>
<td>-0.683</td>
<td>0.496</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.20 ± 0.92</td>
<td>4.10 ± 0.98</td>
<td>0.537</td>
<td>0.593</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.30 ± 0.32</td>
<td>1.35 ± 0.39</td>
<td>-0.717</td>
<td>0.475</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.31 ± 0.29</td>
<td>1.35 ± 0.30</td>
<td>-0.691</td>
<td>0.491</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.24 ± 0.82</td>
<td>2.44 ± 0.91</td>
<td>-1.179</td>
<td>0.241</td>
</tr>
</tbody>
</table>

MPO: Myeloperoxidase; sST2: Soluble ST2; hs-CRP: Hypersensitive C-reactive protein; CK-MB: Creatine kinase isoenzyme; cTnl: Cardiac troponin I; Scr: Serum creatinine; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein; LDL-C: Low-density lipoprotein.

Table 3 Comparison of serum indices such as myeloperoxidase and soluble ST2 in the observation group before and after cardiopulmonary resuscitation

<table>
<thead>
<tr>
<th>Index</th>
<th>Before CPR (n = 54)</th>
<th>After CPR (n = 54)</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPO (ng/L)</td>
<td>2.95 ± 0.89</td>
<td>2.30 ± 0.90</td>
<td>3.701</td>
<td>0.000</td>
</tr>
<tr>
<td>sST2 (pg/L)</td>
<td>115.50 ± 21.10</td>
<td>105.54 ± 17.89</td>
<td>2.586</td>
<td>0.011</td>
</tr>
<tr>
<td>hs-CRP (ng/L)</td>
<td>3.76 ± 0.97</td>
<td>3.01 ± 0.95</td>
<td>3.979</td>
<td>0.000</td>
</tr>
<tr>
<td>Lactic acid (mmol/L)</td>
<td>5.77 ± 0.88</td>
<td>5.15 ± 0.82</td>
<td>3.709</td>
<td>0.000</td>
</tr>
<tr>
<td>CK-MB (U/L)</td>
<td>76.39 ± 8.28</td>
<td>70.40 ± 11.16</td>
<td>3.124</td>
<td>0.002</td>
</tr>
<tr>
<td>cTnl (μg/L)</td>
<td>4.59 ± 0.82</td>
<td>4.02 ± 0.97</td>
<td>3.244</td>
<td>0.002</td>
</tr>
</tbody>
</table>

CPR: Cardiopulmonary resuscitation; MPO: Myeloperoxidase; sST2: Soluble ST2; hs-CRP: Hypersensitive C-reactive protein; CK-MB: Creatine kinase isoenzyme; cTnl: Cardiac troponin I.

DISCUSSION

Brain damage in patients with cardiac arrest is usually caused by abnormal blood flow resulting in systemic ischemia. Since the brain has high oxygen demand and sensitivity to hypoxia, cardiac arrest leads to depolarization of cell membranes and production of free radicals[7,8]. Moreover, free radicals can induce oxidative stress and neuronal damage to a certain extent. Cells will also undergo apoptosis and necrosis, and many metabolites will cross through the blood-brain barrier. Therefore, the prognostic outcome of patients can be evaluated by testing the corresponding serum markers[9-11].

MPO is a type of hemoglobin, an important inflammatory factor, and an important marker of oxidative stress, which plays a significant role in atherosclerosis[12]. Therefore, the increase in MPO will affect the activity of heme oxidase, leading to metabolic disorders of hemoglobin. This further affects the blood oxygen saturation and contributes to the deterioration of an AMI patient’s condition[13]. As a member of the interleukin-1 receptor superfamily, sST2 is mainly expressed in mast cells. In Th2
Table 4 Comparison of serum indices such as myeloperoxidase and soluble ST2 in the observation group between the restoration of spontaneous circulation patients and non-restoration of spontaneous circulation patients

<table>
<thead>
<tr>
<th>Index</th>
<th>ROSC group (n = 24)</th>
<th>Non-ROSC group (n = 30)</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPO (ng/L)</td>
<td>2.71 ± 0.42</td>
<td>3.14 ± 0.47</td>
<td>-3.500</td>
<td>0.001</td>
</tr>
<tr>
<td>sST2 (pg/L)</td>
<td>110.20 ± 15.65</td>
<td>119.90 ± 17.05</td>
<td>-2.154</td>
<td>0.036</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>3.54 ± 0.72</td>
<td>3.97 ± 0.82</td>
<td>-2.020</td>
<td>0.049</td>
</tr>
<tr>
<td>Lactic acid (mmol/L)</td>
<td>5.52 ± 0.70</td>
<td>5.98 ± 0.63</td>
<td>-2.538</td>
<td>0.014</td>
</tr>
<tr>
<td>CK-MB (U/L)</td>
<td>74.43 ± 6.50</td>
<td>78.38 ± 7.10</td>
<td>-2.108</td>
<td>0.040</td>
</tr>
<tr>
<td>cTnl (μg/L)</td>
<td>4.41 ± 0.70</td>
<td>4.81 ± 0.65</td>
<td>-2.172</td>
<td>0.034</td>
</tr>
</tbody>
</table>

ROSC: Restoration of spontaneous circulation; MPO: Myeloperoxidase; sST2: Soluble ST2; hs-CRP: Hypersensitive C-reactive protein; CK-MB: Creatine kinase isoenzyme; cTnl: Cardiac troponin I.

Table 5 Comparison of serum indices such as myeloperoxidase and soluble ST2 in the observation group between the patients who died and survived before cardiopulmonary resuscitation

<table>
<thead>
<tr>
<th>Index</th>
<th>Death (n = 35)</th>
<th>Survival (n = 19)</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPO (ng/L)</td>
<td>3.11 ± 0.58</td>
<td>2.64 ± 0.68</td>
<td>2.676</td>
<td>0.010</td>
</tr>
<tr>
<td>sST2 (pg/L)</td>
<td>120.02 ± 15.30</td>
<td>106.83 ± 16.10</td>
<td>2.971</td>
<td>0.004</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>3.89 ± 0.59</td>
<td>3.50 ± 0.60</td>
<td>2.306</td>
<td>0.025</td>
</tr>
<tr>
<td>Lactic acid (mmol/L)</td>
<td>5.69 ± 0.80</td>
<td>5.19 ± 0.74</td>
<td>2.250</td>
<td>0.029</td>
</tr>
<tr>
<td>CK-MB (U/L)</td>
<td>74.82 ± 6.82</td>
<td>73.68 ± 7.05</td>
<td>0.580</td>
<td>0.565</td>
</tr>
<tr>
<td>cTnl (μg/L)</td>
<td>4.62 ± 0.78</td>
<td>4.53 ± 0.69</td>
<td>0.421</td>
<td>0.675</td>
</tr>
</tbody>
</table>

MPO: Myeloperoxidase; sST2: Soluble ST2; hs-CRP: Hypersensitive C-reactive protein; CK-MB: Creatine kinase isoenzyme; cTnl: Cardiac troponin I.

Table 6 Receiver operating characteristic curve parameters for predicting restoration of spontaneous circulation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Area under curve</th>
<th>P value</th>
<th>Cut off value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPO</td>
<td>0.616</td>
<td>0.039</td>
<td>3.50</td>
<td>40.70</td>
<td>79.60</td>
</tr>
<tr>
<td>sST2</td>
<td>0.681</td>
<td>0.001</td>
<td>121.69</td>
<td>55.90</td>
<td>79.60</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.705</td>
<td>0.000</td>
<td>3.93</td>
<td>64.40</td>
<td>75.50</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>0.704</td>
<td>0.000</td>
<td>5.76</td>
<td>78.00</td>
<td>63.30</td>
</tr>
<tr>
<td>CK-MB</td>
<td>0.702</td>
<td>0.000</td>
<td>76.96</td>
<td>55.90</td>
<td>77.60</td>
</tr>
<tr>
<td>cTnl</td>
<td>0.656</td>
<td>0.005</td>
<td>3.98</td>
<td>86.40</td>
<td>44.90</td>
</tr>
</tbody>
</table>

MPO: Myeloperoxidase; sST2: Soluble ST2; hs-CRP: Hypersensitive C-reactive protein; CK-MB: Creatine kinase isoenzyme; cTnl: Cardiac troponin I.

cells and fibroblasts, its role is mainly for immunomodulatory functions in various inflammatory processes[14,15].

Our study showed that serum levels of MPO and sST2 in AMI patients were significantly higher than those in the control group. Moreover, the levels of MPO and sST2 were significantly decreased after CPR, indicating that MPO and sST2 may participate in the occurrence and development of AMI. Furthermore, in vivo MPO reduces the utilization of nitric oxide in the body, promotes the oxidation of low-density lipoprotein, and accelerates the deposition of cholesterol in the blood vessel wall. These promote endothelial dysfunction, leading to the formation of unstable plaques and adverse cardiovascular events, wherein inflammation is significantly increased. In contrast, after CPR, the blood oxygen saturation, immune inflammation, MPO, and sST2 levels are significantly reduced.
Table 7 Receiver operating characteristic curve parameters for predicting mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Area under curve</th>
<th>P value</th>
<th>Cut off value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPO</td>
<td>0.724</td>
<td>0.000</td>
<td>3.36</td>
<td>54.90</td>
<td>86.50</td>
</tr>
<tr>
<td>sST-2</td>
<td>0.800</td>
<td>0.000</td>
<td>114.52</td>
<td>60.60</td>
<td>91.90</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.689</td>
<td>0.001</td>
<td>3.48</td>
<td>73.20</td>
<td>64.90</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>0.691</td>
<td>0.001</td>
<td>5.39</td>
<td>64.80</td>
<td>70.30</td>
</tr>
</tbody>
</table>

MPO: Myeloperoxidase; sST2: Soluble ST2; hs-CRP: Hypersensitive C-reactive protein.

Table 8 Logistic regression analysis of restoration of spontaneous circulation factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>SE</th>
<th>Walds</th>
<th>P value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPO</td>
<td>0.511</td>
<td>6.938</td>
<td>0.000</td>
<td>1.667 (1.140-2.438)</td>
</tr>
<tr>
<td>sST-2</td>
<td>0.463</td>
<td>11.762</td>
<td>0.000</td>
<td>1.589 (1.219-2.070)</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.343</td>
<td>9.379</td>
<td>0.000</td>
<td>1.409 (1.131-1.755)</td>
</tr>
</tbody>
</table>

OR: Odds ratios; MPO: Myeloperoxidase; sST2: Soluble ST2; hs-CRP: Hypersensitive C-reactive protein.

Table 9 Logistic regression analysis of death factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>SE</th>
<th>Walds</th>
<th>P value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPO</td>
<td>0.485</td>
<td>7.101</td>
<td>0.000</td>
<td>1.624 (1.137-2.320)</td>
</tr>
<tr>
<td>sST-2</td>
<td>0.422</td>
<td>12.163</td>
<td>0.000</td>
<td>1.525 (1.203-1.933)</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.372</td>
<td>11.648</td>
<td>0.000</td>
<td>1.451 (1.172-1.796)</td>
</tr>
<tr>
<td>lactic acid</td>
<td>0.311</td>
<td>6.393</td>
<td>0.000</td>
<td>1.365 (1.072-1.737)</td>
</tr>
</tbody>
</table>

OR: Odds ratios; CI: Confidence interval; MPO: Myeloperoxidase; sST2: Soluble ST2; hs-CRP: Hypersensitive C-reactive protein.

Figure 1 Receiver operating characteristic curve parameters for predicting restoration of spontaneous circulation and mortality. A: Restoration of spontaneous circulation; B: Mortality. MPO: Myeloperoxidase; sST2: Soluble ST2; hs-CRP: Hypersensitive C-reactive protein; CK-MB: Creatine kinase isoenzyme; cTnI: Cardiac troponin I.

Hs-CRP, an acute-phase protein synthesized by the liver, can chemically attract monocytes, induce the production of tissue factors, and promote thrombin[16]. Meanwhile, CRP is also a chemokine of fibrinogen, which enables macrophages to adhere to the endothelial surface and transplant to the intima, causing reactive T lymphocytes accumulation, enhanced platelet activity, imbalance of coagulation and
fibrinolysis systems, and promotion of arterial thrombosis. All these mechanisms can lead to instability and rupture of atherosclerotic plaques, leading to acute coronary syndrome\cite{17}.

CK-MB and cTnI are the main clinical indicators of myocardial injury examination and have a certain reference value in predicting the degree of myocardial ischemia injury. The combined detection of the two can improve early diagnosis rate and degree monitoring in the treatment process\cite{18,19}. Lactic acid is the final product of human anaerobic glycolysis. When tissues are starved of oxygen, they undergo anaerobic metabolism, resulting in elevated levels of lactic acid in the patient’s blood, which can indicate the extent of brain damage\cite{20}.

In our study, the serum levels of sST2, hs-CRP, lactic acid, CK-MB, and cTnI in the observation group were significantly higher than those in the control group \((P < 0.05)\). These indices decreased after CPR \((P < 0.05)\). In addition, the levels of serum MPO, hs-CRP, lactic acid, CK-MB, and cTnI in ROSC patients were significantly lower than those in non-ROSC patients \((P < 0.05)\). The analysis suggests that the myocardium of patients with myocardial infarction has different degrees of damage, coagulation dysfunction, secondary brain injury, cardiac insufficiency, and other symptoms. Therefore, the serum levels of sST2, hs-CRP, lactic acid, CK-MB, and cTnI increased accordingly. When CPR was performed and ROSC occurred, brain injury and myocardial ischemia injury symptoms improved, myocardial contractility significantly increased, and myocardial indices significantly decreased. Thus, serum indicators have a higher value in predicting ROSC and death. Multivariate analysis results showed that MPO, sST2, and hs-CRP were the influencing factors of ROSC, and MPO, SST2, hs-CRP, and lactic acid were the influencing factors of patients’ death, and this is consistent with the findings of previous reports. Thus, these serum indicators could be used as important predictors in clinical research.

Currently, there are no clinical studies that report on changes in serum MPO, sST2, hs-CRP, lactic acid, among others in patients with AMI who had cardiac arrest and CPR. Our study suggests using these objective laboratory indicators to predict ROSC recovery and clinical prognosis of patients with AMI who had CPR.

The limitations of our study include a lack of in-depth research on the corresponding mechanism and its relatively small sample size. Therefore, further in-depth multi-center research with large samples is recommended.

CONCLUSION

The levels of serum MPO, sST2, hs-CRP, and lactic acid were significantly decreased in patients with cardiac arrest caused by AMI after CPR. Moreover, MPO, sST2, hs-CRP, and lactic acid had a certain value in predicting the recovery and prognosis of patients with ROSC.

ARTICLE HIGHLIGHTS

Research background
The minimum target of cardiac resuscitation is the restoration of spontaneous circulation.

Research motivation
Effective clinical evaluation of the prognosis of patients with acute myocardial infarction (AMI) after cardiac resuscitation is of great significance.

Research objectives
This study aimed to explore the effect of cardiopulmonary resuscitation (CPR) on the levels of myeloperoxidase (MPO), soluble ST2 (sST2), and hypersensitive C-reactive protein (hs-CRP) in patients with AMI.

Research methods
A total of 54 AMI patients with cardiac arrest who were managed in our hospital were selected as the observation group. Fifty patients with AMI were selected as the control group.
Research results
Serum levels of MPO, sST2, hs-CRP, lactic acid, creatine kinase isoenzyme, and troponin I were significantly higher in the observation group than in the control group (P < 0.05).

Research conclusions
MPO, sST2, hs-CRP, and lactic acid had a certain value in predicting the recovery and prognosis of patients with restoration of spontaneous circulation.

Research perspectives
Further in-depth multi-center research with large samples is recommended.

REFERENCES
6 Zeymer U. [Diagnosis and initial management of acute myocardial infarction]. MMW Fortschr Med 2019; 161: 34-36 [PMID: 30830611 DOI: 10.1007/s15006-019-0223-3]
Hou M et al. Early cardiopulmonary resuscitation in AMI

31358739 DOI: 10.1038/s41467-019-11255-0


Prospective Study

Remimazolam benzenesulfonate anesthesia effectiveness in cardiac surgery patients under general anesthesia

Fang Tang, Jian-Min Yi, Hong-Yan Gong, Zi-Yun Lu, Jie Chen, Bei Fang, Chen Chen, Zhi-Yi Liu

ORCID number: Fang Tang 0000-0002-8368-5169; Jian-Min Yi 0000-0001-9047-3677; Hong-Yan Gong 0000-0002-1066-4556; Zi-Yun Lu 0000-0002-5373-3297; Jie Chen 0000-0003-1492-1313; Bei Fang 0000-0001-9889-031X; Chen Chen 0000-0001-8712-1961; Zhi-Yi Liu 0000-0002-8505-2568.

Author contributions: Tang F and Yi JM designed the experiment; Gong HY drafted the work; Lu ZY, Chen J and Fang B collected the data; Chen C and Liu ZY analyzed and interpreted data; Tang F, Yi JM and Liu ZY wrote the article.

Institutional review board statement: This study was approved by The First Affiliated Hospital of Nanchang University Ethics Committee.

Clinical trial registration statement: This study is registered at clinical hospital center trial registry. The registration identification number is 2020BL-015-10.

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

Conflict-of-interest statement: The authors declared that there is no conflict of interest.

Data sharing statement: No

Abstract

BACKGROUND
Sedation with propofol injections is associated with a risk of addiction, but remimazolam benzenesulfonate is a comparable anesthetic with a short elimination half-life and independence from cell P450 enzyme metabolism. Compared to remimazolam, remimazolam benzenesulfonate has a faster effect, is more quickly metabolized, produces inactive metabolites and has weak drug interactions. Thus, remimazolam benzenesulfonate has good effectiveness and safety for diagnostic and operational sedation.

AIM
To investigate the clinical value of remimazolam benzenesulfonate in cardiac surgery patients under general anesthesia.

METHODS
A total of 80 patients who underwent surgery in the Department of Cardio-thoracic Surgery from August 2020 to April 2021 were included in the study. Using a random number table, patients were divided into two anesthesia induction groups of 40 patients each: remimazolam (0.3 mg/kg remimazolam benzenesulfonate) and propofol (1.5 mg/kg propofol). Hemodynamic parameters, inflammatory stress response indices, respiratory function indices, perioperative indices and adverse reactions in the two groups were monitored over time for comparison.

RESULTS
At pre-anesthesia induction, the remimazolam and propofol groups did not differ regarding heart rate, mean arterial pressure, cardiac index or volume per wave index. After endotracheal intubation and when the sternum was cut off, mean arterial pressure and volume per wave index were significantly higher in the remimazolam group than in the propofol group ($P < 0.05$). After endotracheal
INTRODUCTION

Open heart surgery under cardiopulmonary bypass (CPB) is the most traumatic surgery conducted in the clinic[1]. When CPB begins, the catecholamine concentration decreases due to the change in the blood perfusion pattern and decrease in blood viscosity, increasing the breadth of anesthesia. Consequently, the patient’s blood pressure decreases. As CPB time increases, the patient’s stress response leads to increased catecholamine secretion and blood viscosity, thereby increasing blood pressure[2,3]. There are different levels of cardiac dysfunction and hemodynamic changes in patients undergoing cardiac surgery. Cardiovascular reserve function in these patients is damaged, making it difficult for them to withstand the effects of anesthetics on circulatory function. Meanwhile, endotracheal intubation during surgery causes a stress response, which is not conducive to effective anesthesia induction[4]. Therefore, to maintain a good depth of anesthesia, understanding how to avoid excessive excitation and sympathetic and parasympathetic nerve inhibition while maintaining hemodynamic stability is key. Thus, choosing suitable anesthesia methods and drugs is crucial. Remimazolam benzenesulfonate, a novel benzodiazepine, is an ultra-short-acting sedative and anesthetic drug that acts on the central y-aminobutyric acid type A receptor to open channels and increase the influx of chloride ions to hyperpolarize nerve membranes and inhibit neuronal activity. Therefore, remimazolam benzenesulfonate is fast-acting and quickly metabolized,

CONCLUSION

Compared with propofol, remimazolam benzenesulfonate benefited cardiac surgery patients under general anesthesia by reducing hemodynamic fluctuations. Remimazolam benzenesulfonate influenced the surgical stress response and respiratory function, thereby reducing anesthesia-related adverse reactions.

Key Words: Anesthesia; Thoracic surgery; Cardiac surgery; Cardiopulmonary bypass; Hemodynamics; Propofol; Drug-related side effects; Adverse reactions

Citation: Tang F, Yi JM, Gong HY, Lu ZY, Chen J, Fang B, Chen C, Liu ZY. Remimazolam benzenesulfonate anesthesia effectiveness in cardiac surgery patients under general anesthesia. World J Clin Cases 2021; 9(34): 10595-10603
URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10595.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10595

Core Tip: Remimazolam benzenesulfonate anesthesia has good effectiveness and safety for diagnostic and operational sedation but has not been evaluated for cardiac surgery. This study investigated the clinical value of remimazolam benzenesulfonate in cardiac surgery patients under general anesthesia. Compared with propofol, remimazolam benzenesulfonate benefitted cardiac surgery patients under general anesthesia by reducing hemodynamic fluctuations and influencing the surgical stress response and respiratory function, thereby reducing anesthesia-related adverse reactions.

CONSORT 2010 statement: The manuscript was checked and revised according to the CONSORT 2010.
Country/Territory of origin: China
Specialty type: Anesthesiology
Provenance and peer review: Unsolicited article; Externally peer reviewed.
Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 1
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0
Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/
Received: July 28, 2021
Peer review started: July 28, 2021
First decision: August 19, 2021
Revised: August 28, 2021
Accepted: October 14, 2021
Article in press: October 14, 2021
Published online: December 6, 2021
P-Reviewer: Fichtner A
S-Editor: Wang JL
L-Editor: Filipodia
P-Editor: Wang JL

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Remimazolam benzenesulfonate anesthesia has good effectiveness and safety for diagnostic and operational sedation but has not been evaluated for cardiac surgery. This study investigated the clinical value of remimazolam benzenesulfonate in cardiac surgery patients under general anesthesia. Compared with propofol, remimazolam benzenesulfonate benefitted cardiac surgery patients under general anesthesia by reducing hemodynamic fluctuations and influencing the surgical stress response and respiratory function, thereby reducing anesthesia-related adverse reactions.

Citation: Tang F, Yi JM, Gong HY, Lu ZY, Chen J, Fang B, Chen C, Liu ZY. Remimazolam benzenesulfonate anesthesia effectiveness in cardiac surgery patients under general anesthesia. World J Clin Cases 2021; 9(34): 10595-10603
URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10595.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10595

INTRODUCTION

Open heart surgery under cardiopulmonary bypass (CPB) is the most traumatic surgery conducted in the clinic[1]. When CPB begins, the catecholamine concentration decreases due to the change in the blood perfusion pattern and decrease in blood viscosity, increasing the breadth of anesthesia. Consequently, the patient’s blood pressure decreases. As CPB time increases, the patient’s stress response leads to increased catecholamine secretion and blood viscosity, thereby increasing blood pressure[2,3]. There are different levels of cardiac dysfunction and hemodynamic changes in patients undergoing cardiac surgery. Cardiovascular reserve function in these patients is damaged, making it difficult for them to withstand the effects of anesthetics on circulatory function. Meanwhile, endotracheal intubation during surgery causes a stress response, which is not conducive to effective anesthesia induction[4]. Therefore, to maintain a good depth of anesthesia, understanding how to avoid excessive excitation and sympathetic and parasympathetic nerve inhibition while maintaining hemodynamic stability is key. Thus, choosing suitable anesthesia methods and drugs is crucial. Remimazolam benzenesulfonate, a novel benzodiazepine, is an ultra-short-acting sedative and anesthetic drug that acts on the central Y-aminobutyric acid type A receptor to open channels and increase the influx of chloride ions to hyperpolarize nerve membranes and inhibit neuronal activity. Therefore, remimazolam benzenesulfonate is fast-acting and quickly metabolized,
making it safe and effective[5,6]. Our study explored the clinical application of remimazolam benzenesulfonate in cardiac surgery patients under general anesthesia.

MATERIALS AND METHODS

Baseline data
In total, 80 patients who underwent surgery in the Department of Cardiothoracic Surgery from August 2020 to April 2021 were included. Patients were divided into two anesthesia groups (remimazolam and propofol) of 40 patients each using a random number table. Patients were included if they were between 19 and 75 years of age, required heart valve replacement surgery by the same medical staff at our hospital, were classified as American Society of Anesthesiologists grades I-III, had a total surgery time of less than 7 h and had normal preoperative liver, kidney and circulation functions. Patients were excluded if they had coagulation dysfunction, hypertension, anemia, acute myocardial infarction, viral myocarditis, atrioventricular block, cerebrovascular disease or poor blood glucose control.

Before commencement, the study plan was approved by the Medical Ethics Committee of our hospital, and the patients and their families signed informed consent forms.

Anesthesia methods
The remimazolam group received 0.3 mg/kg of remimazolam benzenesulfonate (Yichang Renfu Pharmaceutical Group Co. Ltd., Yichang, Hubei, China) for anesthesia induction within 30 s. If the bispectral index value was ≤ 60, then 0.2 mg/kg of cisatracurium (Jiangsu Hengrui Pharmaceutical Co. Ltd., Jiangsu Province, China) and 4 μg/kg of fentanyl (Yichang Renfu Pharmaceutical Co. Ltd.) were intravenously injected. Endotracheal intubation was performed after meeting the condition.

The propofol group received 1.5 mg/kg of propofol (Xi’an Libang Pharmaceutical Co., Ltd., Xi’an, Shaanxi, China) for anesthesia induction within 30 s. If bispectral index value was ≤ 60, then 0.2 mg/kg of cisatracurium and then 4 μg/kg of fentanyl were intravenously injected. Endotracheal intubation was performed after meeting the condition.

Observation indices and detection methods
Heart rate (HR), mean arterial pressure (MAP), cardiac index, volume per wave index (SVI), respiratory index (RI), serum interleukin-6 (IL-6) level, tumour necrosis factor alpha (TNF-α), norepinephrine (NE) level, epinephrine (E) level, cortisol (COR) level and blood glucose (GLU) level were measured preoperatively and 12 h postoperatively. Perioperative indicators, such as operative time, operative blood loss, intraoperative urine volume, CPB turnaround time, ascending aorta occlusion time, recovery time, extubation time, fluid volume and fentanyl dosage, were also recorded. Adverse reaction incidences were also recorded at different times [pre-anesthesia induction, after endotracheal intubation (T1), when the sternum was cut off (T2) and when the machine was shut down] to compare the two groups.

Not all patients needed medication before surgery. During the operation, an HP multifunction monitor (Philips Medical Systems, Germany) continuously monitored the patient’s hemodynamic parameters, and GLU values were measured by arterial blood gas analysis. At each time point, 4 mL of arterial blood was extracted and centrifuged in a centrifuge with an 18-cm radius at a rotation speed of 2500 r/min for 15 min. The serum was separated and then stored at -20 °C. Serum testing was performed using a kit (Beijing North Institute of Biotechnology), following the manufacturer’s instructions. NE and E plasma concentrations were determined by high-performance liquid chromatography. The RI and OI were calculated as follows:

\[ OI = \frac{PaO_2}{FiO_2} \]
\[ RI = \frac{P(A-a)O_2}{PaO_2} \]

Statistical analyses
The estimated HR, MAP, cardiac index and SVI values were tested by normal distribution test, and all were in line with approximately normal distribution or normal distribution, represented by mean ± SD; t-tests were performed for comparisons between the groups. Enumeration data are expressed as percentages, and the χ² test was performed for comparison. SPSS version 21.0 (BM Corp., Armonk, NY, United States) was used for data processing with a test level of α = 0.05.
RESULTS

**Comparison of baseline conditions**
Age, body mass index, blood pressure, HR, GLU, gender and the American Society of Anesthesiologists grade did not differ between the remimazolam and propofol groups ($P > 0.05$; Table 1).

**Comparison of hemodynamic parameter**
At pre-anesthesia induction, HR, MAP, cardiac index and SVI did not differ between the remimazolam and propofol groups ($P > 0.05$). At T1 and T2, MAP and SVI were significantly higher in the remimazolam group than in the propofol group ($P < 0.05$; Table 2).

**Comparison of OI and RI**
At T1, OI and RI did not differ between the remimazolam and propofol groups ($P > 0.05$). At T1 and T2, OI was significantly higher in the remimazolam group than in the propofol group ($P < 0.05$; Table 3).

**Comparison of inflammatory serum markers**
Serum IL-6 and TNF-α did not differ preoperatively or 2 h postoperatively between the remimazolam and propofol groups ($P > 0.05$). However, serum IL-6 and TNF-α were significantly higher in two groups 12 h after surgery compared to those before surgery ($P < 0.05$). Before surgery, NE, E, COR and GLU levels did not differ between the remimazolam and propofol groups ($P > 0.05$); however, 2 h after surgery, the E, COR and GLU levels were significantly higher in the remimazolam group than in propofol group ($P < 0.05$; Table 4).

**Comparison of perioperative indicators**
The operative time, operative blood loss, intraoperative urine volume, CPB transit time, ascending aorta occlusion time, fluid volume and fentanyl dosage did not differ between the two groups ($P > 0.05$). The recovery time and extubation time were significantly lower in the remimazolam group than in the propofol group ($P < 0.05$; Table 5).

**Comparison of adverse reactions**
There were significantly fewer adverse reactions in the remimazolam group (10.00%) than in the propofol group (30.00%) ($P < 0.05$; Table 6).

DISCUSSION
A series of experiments in China and abroad have demonstrated that using anesthetics, such as propofol, during the perioperative period can maintain hemodynamic stability by reducing the release of catecholamines and inflammatory factors[7-10]. In our study, at T1 and T2, MAP and SVI were higher in the remimazolam group than in the propofol group ($P < 0.05$), indicating that remimazolam benzenesulfonate had little effect on intraoperative hemodynamics. This may be because remimazolam benzenesulfonate can act on adrenergic receptors, inhibit NE release, reduce the catecholamine level as well as sympathetic nerve excitability, accelerate atrioventricular conduction and enhance myocardial contractility.

OI is a convenient measurement because it correlates well with hypoxia in the body and reflects the blood flow to the lungs. As such, it is the most commonly used index for monitoring lung oxygenation[11]. During cardiac surgery, the lung is often damaged, and the lung injury mechanism from cardiopulmonary bypass is complex[12]. In our study, at T2 (when the sternum was cut off) and when the machine was shut down, the OI in the remimazolam group was significantly higher than in the propofol group ($P < 0.05$), consistent with the literature[13,14]. This suggests that the intraoperative lung ventilation strategy and remimazolam benzenesulfonate use improve one-lung ventilation oxygenation and lung function, reduce pulmonary complications and have a protective effect on the lungs.

TNF-α is a substance that appears early in lung inflammation and has an important role in the pathological process of lung injury by stimulating the release of inflammatory mediators, such as IL-6 and IL-8[15]. IL-6 is involved in early inflammatory...
Table 1 Comparison of the baseline conditions between the two groups

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Remimazolam group (n = 40)</th>
<th>Propofol group (n = 40)</th>
<th>t/χ² value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54.9 ± 8.5</td>
<td>52.7 ± 7.0</td>
<td>1.264</td>
<td>0.210</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1 ± 2.4</td>
<td>23.9 ± 2.2</td>
<td>0.389</td>
<td>0.699</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>126.3 ± 6.3</td>
<td>124.8 ± 8.1</td>
<td>0.925</td>
<td>0.358</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75.7 ± 6.0</td>
<td>76.5 ± 7.3</td>
<td>-0.535</td>
<td>0.594</td>
</tr>
<tr>
<td>Heart rate (times/min)</td>
<td>76.7 ± 7.1</td>
<td>78.2 ± 7.7</td>
<td>-0.906</td>
<td>0.368</td>
</tr>
<tr>
<td>Blood glucose (mmol/L)</td>
<td>5.39 ± 0.51</td>
<td>5.50 ± 0.48</td>
<td>-0.993</td>
<td>0.324</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 (62.50)</td>
<td>20 (50.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (37.50)</td>
<td>20 (50.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA grades, n (%)</td>
<td>Grade I</td>
<td>Grade II</td>
<td>Grade III</td>
<td>1.868</td>
</tr>
<tr>
<td></td>
<td>8 (20.00)</td>
<td>6 (15.00)</td>
<td>20 (50.00)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 (50.00)</td>
<td>26 (65.00)</td>
<td>8 (20.00)</td>
<td></td>
</tr>
</tbody>
</table>

ASA: American Society of Anesthesiologists; BMI: Body mass index.

response and tissue damage; its expression level is related to the severity and duration of the inflammatory response[16]. Thus, it is an important indicator of the body’s overall inflammatory and stress responses. In this study, we demonstrated that remimazolam benzenesulfonate anesthesia induction effectively reduced systemic inflammatory and oxidative stress responses in patients undergoing thoracoscopic cardiac surgery. The possible mechanisms are activated αo adrenergic receptors and inhibited nuclear factor kappa-B. Additionally, remimazolam benzenesulfonate maintained hemodynamic stability, only reducing the release of inflammatory mediators to a certain extent. In this study, the recovery time and extubation time of patients in the remimazolam group were significantly lower than in the propofol group, indicating that remimazolam benzenesulfonate maintained circulation as well as oxygen supply and demand balance. Remimazolam benzenesulfonate had a more stable and better effect on systemic circulation.

When a stress response occurs, the catecholamines secreted by the hypothalamic-pituitary-adrenal axis are excited to stimulate the locus coeruleus-sympathetic nerve-adrenal medulla system to produce E, NE and other hormones, which are used as indicators of the sensitivity and specificity of the stress response[17,18]. In this study, 2 h after surgery, the increase of E and COR were significantly lower in the remimazolam group than in the propofol group. This indicated that the increase of plasma E and COR concentrations could be inhibited and the stress response of patients could be reduced. Possible reasons for the elevated index were related to the continuous pumping of adrenaline after surgery and tracheal tube stimulation as the patient gradually woke up. There was an increasing trend in the NE concentration in both groups, though it was statistically insignificant and the specific reasons need to be further studied.

GLU is the main source of various tissues and cells in the body. A high GLU concentration during the perioperative period reduces the mitochondrial function in cells, destroys cell structures, affects inflammatory cell movement to the affected area, increases the infection surgical incision rate and affects wound healing[19]. When the body is in a stress response state, a large number of stress hormones, cytokines and inflammatory mediators are produced and released, making the tissue less sensitive to insulin, and thus, less insulin is secreted. As a result, glycogen decomposition and gluconeogenesis are enhanced. This results in a weakened ability to absorb and utilize GLU, which leads to an increase in GLU[20]. In this study, 2 h after surgery, the increase in GLU was significantly lower in the remimazolam group than in the propofol group (P < 0.05), verifying that intraoperative anesthesia induced by remimazolam benzenesulfonate maintained GLU stability during the perioperative period. Adverse reaction incidences were also significantly fewer in the remimazolam group than in the propofol group, suggesting that remimazolam benzenesulfonate is
Table 2 Comparison of the hemodynamic parameter between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Indicators</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (times/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remimazolam group</td>
<td>76.7 ± 7.1</td>
<td>68.3 ± 6.5</td>
<td>66.8 ± 5.9</td>
<td>78.8 ± 6.6</td>
</tr>
<tr>
<td>Propofol group</td>
<td>78.2 ± 7.7</td>
<td>66.7 ± 6.7</td>
<td>65.1 ± 6.0</td>
<td>80.5 ± 7.3</td>
</tr>
<tr>
<td>t value</td>
<td>-0.906</td>
<td>1.091</td>
<td>1.278</td>
<td>-1.093</td>
</tr>
<tr>
<td>P value</td>
<td>0.368</td>
<td>0.279</td>
<td>0.205</td>
<td>0.278</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remimazolam group</td>
<td>98.4 ± 5.3</td>
<td>88.3 ± 4.7</td>
<td>86.7 ± 4.2</td>
<td>102.1 ± 4.8</td>
</tr>
<tr>
<td>Propofol group</td>
<td>99.6 ± 4.7</td>
<td>86.0 ± 4.4</td>
<td>83.8 ± 4.5</td>
<td>103.8 ± 4.2</td>
</tr>
<tr>
<td>t value</td>
<td>-1.071</td>
<td>2.259</td>
<td>2.980</td>
<td>-1.686</td>
</tr>
<tr>
<td>P value</td>
<td>0.287</td>
<td>0.027</td>
<td>0.004</td>
<td>0.096</td>
</tr>
<tr>
<td>CI (L/min m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remimazolam group</td>
<td>3.67 ± 0.62</td>
<td>3.52 ± 0.52</td>
<td>3.56 ± 0.48</td>
<td>3.57 ± 0.53</td>
</tr>
<tr>
<td>Propofol group</td>
<td>3.80 ± 0.60</td>
<td>3.40 ± 0.48</td>
<td>3.51 ± 0.50</td>
<td>3.65 ± 0.49</td>
</tr>
<tr>
<td>t value</td>
<td>-0.953</td>
<td>1.072</td>
<td>0.639</td>
<td>-0.701</td>
</tr>
<tr>
<td>P value</td>
<td>0.344</td>
<td>0.287</td>
<td>0.525</td>
<td>0.485</td>
</tr>
<tr>
<td>SVI (mL/m² bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remimazolam group</td>
<td>47.83 ± 5.81</td>
<td>43.80 ± 5.26</td>
<td>41.94 ± 5.57</td>
<td>45.80 ± 5.16</td>
</tr>
<tr>
<td>Propofol group</td>
<td>49.20 ± 5.63</td>
<td>40.38 ± 4.95</td>
<td>38.53 ± 4.86</td>
<td>43.73 ± 5.57</td>
</tr>
<tr>
<td>t value</td>
<td>-1.071</td>
<td>2.995</td>
<td>2.918</td>
<td>1.724</td>
</tr>
<tr>
<td>P value</td>
<td>0.287</td>
<td>0.004</td>
<td>0.005</td>
<td>0.089</td>
</tr>
</tbody>
</table>

CI: Cardiac index; HR: Heart rate; MAP: Mean arterial pressure; SVI: Volume per wave index; T0: Pre-anesthesia induction; T1: After endotracheal intubation; T2: When the sternum was cut off; T3: When the machine was shut down.

Table 3 Comparison of oxygenation index and respiratory index between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Indicators</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OI (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remimazolam group (n = 40)</td>
<td>398.6 ± 24.7</td>
<td>357.6 ± 28.0</td>
<td>381.8 ± 30.0</td>
</tr>
<tr>
<td>Propofol group (n = 40)</td>
<td>390.1 ± 26.3</td>
<td>338.1 ± 30.5</td>
<td>359.4 ± 33.8</td>
</tr>
<tr>
<td>t value</td>
<td>1.490</td>
<td>2.979</td>
<td>3.135</td>
</tr>
<tr>
<td>P value</td>
<td>0.140</td>
<td>0.004</td>
<td>0.002</td>
</tr>
<tr>
<td>RI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remimazolam group (n = 40)</td>
<td>0.59 ± 0.17</td>
<td>0.90 ± 0.23</td>
<td>0.50 ± 0.18</td>
</tr>
<tr>
<td>Propofol group (n = 40)</td>
<td>0.62 ± 0.17</td>
<td>0.94 ± 0.21</td>
<td>0.56 ± 0.20</td>
</tr>
<tr>
<td>t value</td>
<td>-0.789</td>
<td>-0.812</td>
<td>-1.410</td>
</tr>
<tr>
<td>P value</td>
<td>0.432</td>
<td>0.419</td>
<td>0.162</td>
</tr>
</tbody>
</table>

OI: Oxygenation index; RI: Respiratory index; T1: After endotracheal intubation; T2: When the sternum was cut off; T3: When the machine was shut down.

safe and can make patients feel at ease, resulting in active cooperation with medical staff during treatment.
Currently, remimazolam benzenesulfonate has not been clinically used to induce anesthesia in cardiac surgery. However, remimazolam benzenesulfonate has a good anesthesia effect and is commonly used for clinical treatments and diagnostic
Tang F et al. Remimazolam effectiveness in cardiac surgery

Table 4 Comparison of the serum levels of inflammatory factors between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Remimazolam group (n = 40)</th>
<th>Propofol group (n = 40)</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>1.63 ± 0.46</td>
<td>1.80 ± 0.50</td>
<td>-1.583</td>
<td>0.118</td>
</tr>
<tr>
<td>12 h after surgery</td>
<td>3.74 ± 0.95</td>
<td>3.98 ± 1.03</td>
<td>-1.083</td>
<td>0.282</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>54.83 ± 12.30</td>
<td>50.11 ± 10.86</td>
<td>1.819</td>
<td>0.073</td>
</tr>
<tr>
<td>12 h after surgery</td>
<td>87.55 ± 15.40</td>
<td>90.28 ± 14.81</td>
<td>-1.696</td>
<td>0.094</td>
</tr>
<tr>
<td>E (pg/μL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>1.58 ± 0.38</td>
<td>1.49 ± 0.40</td>
<td>1.032</td>
<td>0.305</td>
</tr>
<tr>
<td>12 h after surgery</td>
<td>2.52 ± 0.70</td>
<td>2.86 ± 0.76</td>
<td>-2.081</td>
<td>0.041</td>
</tr>
<tr>
<td>NE (pg/μL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>2.66 ± 0.48</td>
<td>2.48 ± 0.51</td>
<td>1.625</td>
<td>0.108</td>
</tr>
<tr>
<td>12 h after surgery</td>
<td>3.38 ± 0.75</td>
<td>3.73 ± 0.88</td>
<td>-1.914</td>
<td>0.059</td>
</tr>
<tr>
<td>COR (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>22.73 ± 4.81</td>
<td>21.40 ± 4.36</td>
<td>1.296</td>
<td>0.199</td>
</tr>
<tr>
<td>12 h after surgery</td>
<td>34.20 ± 6.85</td>
<td>31.06 ± 5.72</td>
<td>2.225</td>
<td>0.029</td>
</tr>
<tr>
<td>GLU (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>5.39 ± 0.51</td>
<td>5.50 ± 0.51</td>
<td>-0.993</td>
<td>0.324</td>
</tr>
<tr>
<td>12 h after surgery</td>
<td>6.18 ± 0.62</td>
<td>6.54 ± 0.75</td>
<td>-2.34</td>
<td>0.022</td>
</tr>
</tbody>
</table>

COR: Cortisol; E: Epinephrine; GLU: Glucose; IL-6: Interleukin-6; NE: Norepinephrine; TNF-α: Tumor necrosis factor alpha.

Table 5 Comparison of the perioperative indicators between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Remimazolam group (n = 40)</th>
<th>Propofol group (n = 40)</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time (min)</td>
<td>249.6 ± 18.5</td>
<td>245.8 ± 17.0</td>
<td>0.957</td>
<td>0.342</td>
</tr>
<tr>
<td>Operative blood loss (mL)</td>
<td>308.4 ± 20.7</td>
<td>304.1 ± 18.6</td>
<td>0.977</td>
<td>0.331</td>
</tr>
<tr>
<td>Intraoperative urine volume (mL)</td>
<td>488.3 ± 81.0</td>
<td>502.7 ± 86.5</td>
<td>-0.769</td>
<td>0.444</td>
</tr>
<tr>
<td>CPB transit time (min)</td>
<td>115.8 ± 9.8</td>
<td>113.5 ± 10.6</td>
<td>1.008</td>
<td>0.317</td>
</tr>
<tr>
<td>Ascending aorta occlusion time (min)</td>
<td>76.4 ± 5.1</td>
<td>78.1 ± 6.3</td>
<td>-1.326</td>
<td>0.189</td>
</tr>
<tr>
<td>Recovery time (min)</td>
<td>121.1 ± 18.0</td>
<td>140.2 ± 21.5</td>
<td>-4.308</td>
<td>0.000</td>
</tr>
<tr>
<td>Extubation time (min)</td>
<td>158.3 ± 24.7</td>
<td>174.9 ± 28.6</td>
<td>-2.778</td>
<td>0.007</td>
</tr>
<tr>
<td>Fluid volume (mL)</td>
<td>1985.6 ± 223.1</td>
<td>2056.7 ± 245.7</td>
<td>-1.355</td>
<td>0.179</td>
</tr>
<tr>
<td>Fentanyl dosage (mg)</td>
<td>122.8 ± 21.6</td>
<td>126.4 ± 34.2</td>
<td>-0.563</td>
<td>0.575</td>
</tr>
</tbody>
</table>

CPB: Cardiopulmonary bypass.

operations. This study explored the anesthetic effect and safety of remimazolam benzenesulfonate-induced anesthesia by comparing it with propofol in patients who underwent cardiac surgery under general anesthesia to provide more information for creating clinical anesthesia plans.

CONCLUSION

Compared with propofol, anesthetic induction with remimazolam benzenesulfonate in
cardiac surgery patients under general anesthesia was better at reducing hemodynamic fluctuations caused by surgery, surgical stress response and anesthetic influence on respiratory function, thereby reducing anesthetic-related adverse reactions.

### ARTICLE HIGHLIGHTS

#### Research background

Compared to remimazolam, remimazolam benzenesulfonate has a faster effect, is more quickly metabolized, produces inactive metabolites and has weak drug interactions. Remimazolam benzenesulfonate has good effectiveness and safety for diagnostic and operational sedation.

#### Research motivation

This study investigated the clinical value of remimazolam benzenesulfonate in cardiac surgery patients under general anesthesia.

#### Research objectives

In order to explore the clinical value of remimazolam benzenesulfonate under general anesthesia in patients undergoing cardiac surgery.

#### Research methods

In total, 80 patients who underwent surgery were included in the study. Using a random number table, patients were divided into two anesthesia induction groups of 40 patients each: Remimazolam and propofol. Hemodynamic parameters, inflammatory stress response indices, respiratory function indices, perioperative indices and adverse reactions in the two groups were monitored over time for comparison.

#### Research results

At pre-anesthesia induction, the remimazolam and propofol groups did not differ regarding heart rate, mean arterial pressure, cardiac index or volume per wave index. After endotracheal intubation and when the sternum was cut off, mean arterial pressure and volume per wave index were significantly higher in the remimazolam group than in the propofol group. After endotracheal intubation, the oxygenation index and the respiratory index did not differ between the groups. After endotracheal intubation and when the sternum was cut off, the oxygenation index values were significantly higher in the remimazolam group than in the propofol group. Serum interleukin-6 and tumor necrosis factor-α levels 12 h after surgery were significantly higher than before surgery in both groups.

#### Research conclusions

The results suggest that compared with propofol, remimazolam benzenesulfonate benefited cardiac surgery patients under general anesthesia by reducing hemodynamic fluctuations.

#### Research perspectives

Remimazolam benzenesulfonate can affect surgical stress response and respiratory function, thereby reducing adverse reactions related to anesthesia and has greater clinical promotion value.
REFERENCES


Effects of lower body positive pressure treadmill on functional improvement in knee osteoarthritis: A randomized clinical trial study

Hong-Xin Chen, Yao-Xuan Zhan, Hai-Ning Ou, Yao-Yao You, Wan-Ying Li, Shan-Shan Jiang, Mei-Feng Zheng, Lin-Zi Zhang, Ke Chen, Qiu-Xia Chen

Abstract

BACKGROUND
Knee joint pain and stiffness are the two main symptoms of knee osteoarthritis (OA) and thus restrict a patient’s activities, such as walking and walking up and downstairs. The lower body positive pressure (LBPP) treadmill as one of the emerging body weight support system devices brings new hope for exercise-related rehabilitation for knee OA patients.

AIM
To investigate the biomechanical effects and the subjective clinical assessment of LBPP treadmill walking exercise when compared with conventional therapy in mild to moderate knee OA patients.
INTRODUCTION

Osteoarthritis (OA), the most common rheumatic disease, primarily affects the articular cartilage and the subchondral bone of a synovial joint and eventually results in joint failure[1]. Knee joint pain and stiffness are the two main symptoms of knee OA and thus restrict a patient’s activities, such as walking and walking up and down stairs. Usually, pain limits the patient’s ability to move, and the reduction in lower extremity activity will exacerbate the decline of joint muscle function thus producing a vicious cycle. Ways to help the patient recover lower limb joint activity to the maximum possible level become the key to breaking this vicious cycle[2]. Numerous international clinical practice guidelines of knee OA provide growing evidence to support exercise as a form of management of non-pharmacological interventions for knee OA patients[2-4]. Previous studies report exercise has similar management-
related effects as seen with analgesics and non-steroidal anti-inflammatory drugs but without contraindications or side effects[5,6].

As one of the emerging body weight support system devices, a lower body positive pressure (LBPP) treadmill brings new hope for exercise-related rehabilitation for knee OA patients[7]. The system uses a sealed inflatable positive pressure chamber at a waist-level high to achieve accurate weight support of the lower extremities (20%-100% in 1% increments) to reduce knee pressure and pain related to the pathology of osteophyte formation and joint cavity stenosis[8,9]. The clinical effect of LBPP in knee OA clinical rehabilitation was affirmed[10-12], but the relative mechanism of biomechanical influence on the rehabilitation of lower limb function in knee OA patients is not yet clear. Moreover, to our best knowledge, there are no randomized controlled trials (RCT) focusing on LBPP training effects on knee OA rehabilitation, and only several studies use subjective clinical assessments[13]. Thus, the purpose of our RCT study was to investigate the biomechanical effects and the subjective clinical assessment of LBPP treadmill walking exercise when compared with conventional therapy in mild to moderate knee OA patients. We hypothesized that both LBPP training and conventional training could improve the clinical symptoms and gait parameters of knee OA, but the LBPP group might have a more significant effect.

MATERIALS AND METHODS

Patient recruitment
All the subjects were recruited from the Department of Rehabilitation Medicine at the Fifth Affiliated Hospital of Guangzhou Medical University from July 2017 to July 2019. The inclusion criteria consisted of knee OA diagnosis based on the diagnostic criteria of the American College of Rheumatology in 2001: (1) Subjects aged 50-years-old to 75-years-old; (2) Conformed with Kellgren-Lawrence Grade II or III[14] of knee joint OA; (3) Without plans to take any pain killers during this inpatient point; (4) Without cognitive and comprehension impairment following a mini-mental state examination > 26 points; and (5) Signed informed consent. The exclusion criteria consisted of several parameters: (1) Unstable vital signs (i.e. high blood pressure and tachycardia), combined with heart, brain, blood vessel, spirit, liver, kidney, and other serious diseases that affect daily activities; (2) Combined with knee joint tuberculosis, tumors, and other diseases that affect knee function; (3) Combined with rheumatism, gout, severe osteoporosis, and other diseases that affect joint pain and lower limb mobility; (4) Cannot tolerate the experiment; and/or (5) Refused to sign the informed consent. In the cases of bilateral knee OA, the more symptomatic knee was designated as the affected knee. The participant was instructed to base their responses on only the affected knee for the purpose of pre- and post-assessments[15].

Study design
This study was designed as a prospective, single-center, randomized pilot study. This study was registered at the China Clinical Trial Registration Centre (No. ChiCTR 1800017677) and approved by the Medical Ethics Association of the Fifth Affiliated Hospital of Guangzhou Medical University (No. KY01-2018-10-18).

Interventions
The eligible knee OA patients were randomly assigned to two groups based on the computer-generated random numbers list (LBPP group and control group). The entire training session was supervised by a trained physiotherapist for guidance and safety. The patients in the LBPP group (experimental treatment group) performed an LBPP walking training program (provided using AlterG M320 Antigravity Treadmill, California, USA) for 30 min/session/day, 6 d/week for 2 wk, which was based on our previous study[11]. The LBPP walking protocol included 20 min walking stage (speed = 1.5–2.0 mph, BW = 65%, Incline = 0%) and 10 min warm-up and cooling down stage at the beginning and ending of the session (Figure 1B). The patients were allowed to use handrails during LBPP treadmill training to help them keep their balance. Before the LBPP walking training, the physiotherapist checked the patient’s blood pressure (BP) and heart rate (HR) using an electronic blood pressure monitor (Omron-U10L, Omron Healthcare Co., Ltd., China) to make sure the patient was in optimum condition for exercise (60 bpm ≤ HR ≤ 120 bpm and 90/60 mmHg ≤ BP ≤ 160/100 mmHg). When the patient stood into the LBPP treadmill, the calculation would be run automatically before training started. And during the LBPP walking training, the safety lanyard supplied with the LBPP treadmill should be attached to the patient’s
clothing for emergency stops during the training process in case the patient falls or does not feel well (Figure 1A). The patients in the control group (conventional treatment group) performed walking on the indoor ground at a self-selected speed for 30 min/session per day, 6 d per week for 2 wk. The control group (conventional treatment group) performed walking on the indoor ground at a self-selected speed for 30 min/session per day, 6 d per week for 2 wk. Each walking session consisted of 5-min walking and 5-min seated rest for 3 cycles. Moreover, during walking, the physical therapist guided the patient to keep the range of motion of the knee joint at 0-15° to make the heel fully contact the ground. The patients were allowed to use any assistive device (i.e. canes, crutches, and walkers) during walking to help them keep balance. Each group (LBPP group and control group) understood that they would complete 12 sessions for the total amount using the same venue. Meanwhile, both groups maintained the same amount of conventional physiotherapy and manual therapy daily based on the clinical guidelines of knee OA[2].
Assessments
All patients underwent clinical assessments and gait analysis at pre- and 2-wk post-treatment time points. The assessment method was based on our previous study.[11] Lower limb function and mobility for knee OA patients were measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) with five items for pain, two items for stiffness, and 17 functional items.[16] Total scores range from 0 (complete disability) to 100 (no disability). Subjective pain was evaluated using the visual analog scale (VAS) ranging from 0 (no pain) to 10 (severe pain). The active knee joint range-of-motion (AROM) was measured using a handheld 2-arm goniometer.[17] Independence in activities of daily living (ADL) was assessed by modified Barthel index[18] and total scores range from 0 (complete dependent) to 100 (complete independent). Gait analysis was performed using the BTS Smart DX 7000 (Bioengineering Technology System, Milan, Italy). Twenty-two spherical markers were positioned bilaterally on the patient’s anatomical landmarks based on the Davis protocol[19]. The patients were instructed to stand straight for 30 sec, which represented the standing phase, and then walk with a self-selected speed along the walkway five times as the walking phase. Temporo-spatial parameters and knee flexion/extension trajectory in the gait cycle were recorded and included in statistical analysis. Calibration of the gait analysis system was performed by the designated lab member every week to make sure data acquisition was accurate. The primary outcomes were gait parameters, which were used to evaluate gait performance/walking ability. The second outcomes were clinical assessment scales, which were used to represent symptom improvement.

To calculate the statistical power, we set the standardized difference of the primary outcome (gait velocity) to be equal to 0.2, and the dropout rate to be equal to 20%.[20] The sample size for each group should be more than nine.

Statistical analysis
All statistical analyses were conducted using IBM SPSS 25.0 software. Parametric data were presented as means ± SD if normally distributed or median if not. Counting and grade data were presented as ratios. Baseline characteristics and post-treatment outcome measures between groups were compared using independent t-tests. Pre- and post-treatment outcome measures within the group were compared using the paired-t-test. Measurement data that do not conform to the normal distribution and the uniformity of variance were compared using the nonparametric rank-sum Mann-Whitney U test. The test level was statistically significant at P < 0.05.

RESULTS
A total of twenty patients, of whom ten were allocated into the LBPP group and ten were allocated into the control group, were screened for this study. Two patients in the LBPP group were discharged early for family reasons and nobody was dropped out because of intolerance for the whole process (Figure 2). The basic characteristics of the patients in each group are displayed in Table 1. The mean age of each group was 59.63 ± 8.40-years-old in the LBPP group vs 58.30 ± 8.54-years-old in the control group. The body mass index (BMI) was 23.24 ± 0.85 in the LBPP group vs 23.02 ± 1.37 in the control group. The baseline Kellgren-Lawrence grade was 2.25 ± 0.45 in the LBPP group vs 2.30 ± 0.48 in the control group. No significant differences in age, BMI, gender ratio, and Kellgren-Lawrence grade at baseline between the two groups were noted.

The comparison results of clinical assessments are shown within-group (pre-treatment vs post-treatment) or between two groups (LBPP group vs control group) in Table 2 and Figure 3. No significant differences in WOMAC, VAS, Knee AROM flex-extension, or ADL at baseline (pre-treatment timepoint) between the two groups were noted. For comparisons within-group between pre- and post-treatment, WOMAC scores of patients in both groups were found to decrease significantly in the post-treatment timepoint (LBPP group: 70.25 ± 13.93 vs 40.50 ± 11.86, P < 0.001; control group: 69.20 ± 8.88 vs 48.10 ± 8.67, P < 0.001), VAS scores of the patients in both groups were found to have decreased significantly in the post-treatment point (LBPP group: 3.88 ± 0.99 vs 1.63 ± 0.52, P < 0.001; control group: 3.80 ± 0.79 vs 2.60 ± 0.70, P < 0.001), and knee AROM flex-extension of the patients in both groups were found to have increased significantly in the post-treatment point (LBPP group: 112.50 ± 10.13 vs 119.88 ± 8.71, P < 0.001; control group: 110.00 ± 7.69 vs 115.70 ± 7.50, P < 0.001). For comparisons of post-treatment parameters among groups between the LBPP group
Table 1 Baseline characteristics of recruited patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LBPP group (n = 8)</th>
<th>Conventional group (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59.63 ± 8.40</td>
<td>58.30 ± 8.54</td>
<td>0.746</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>3/7</td>
<td>2/6</td>
<td>1.000</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.25 ± 5.23</td>
<td>162.80 ± 5.12</td>
<td>0.825</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.25 ± 4.57</td>
<td>61.11 ± 6.07</td>
<td>0.958</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.24 ± 0.85</td>
<td>23.02 ± 1.37</td>
<td>0.178</td>
</tr>
<tr>
<td>Duration of symptoms (mo)</td>
<td>68.13 ± 14.60</td>
<td>63.40 ± 15.00</td>
<td>0.983</td>
</tr>
<tr>
<td>Affected knee (left/right)</td>
<td>3/5</td>
<td>4/6</td>
<td>1.000</td>
</tr>
<tr>
<td>Kellgren-Lawrence Grade (Grade 2/Grade 3)</td>
<td>6/8</td>
<td>7/3</td>
<td>0.897</td>
</tr>
</tbody>
</table>

There were no significant differences between lower body positive pressure group and conventional group. BMI: Body mass index; LBPP: Lower body positive pressure.

Table 2 Comparisons of clinical assessment parameters within group (between pre- and post-treatment) and among groups (between lower body positive pressure group and conventional group)

<table>
<thead>
<tr>
<th></th>
<th>LBPP group</th>
<th>Conventional group</th>
<th>P value</th>
<th>P value</th>
<th>P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC (scores)</td>
<td>70.25 ± 13.93</td>
<td>40.50 ± 11.86</td>
<td>69.20 ± 8.88</td>
<td>48.10 ± 8.67</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>VAS (scores)</td>
<td>3.88 ± 0.99</td>
<td>1.63 ± 0.52</td>
<td>3.80 ± 0.79</td>
<td>2.60 ± 0.70</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Knee AROM (degree)</td>
<td>112.50 ± 10.13</td>
<td>119.88 ± 8.71</td>
<td>110.00 ± 7.69</td>
<td>115.70 ± 7.50</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ADL (scores)</td>
<td>92.50 ± 5.98</td>
<td>94.38 ± 5.63</td>
<td>91.50 ± 4.74</td>
<td>93.00 ± 4.22</td>
<td>0.197</td>
<td>0.081</td>
</tr>
</tbody>
</table>

1Stands for comparison within lower body positive pressure (LBPP) group between pre-treatment and post-treatment.
2Stands for comparison within conventional group between pre-treatment and post-treatment.
3Stands for comparison among groups for pre-treatment between LBPP group and conventional group.
4Stands for comparison among groups for post-treatment between LBPP group and Conventional group.

LBPP: Lower body positive pressure; WOMAC: Western Ontario and McMaster Universities Index; VAS: Visual analogue scale; AROM: Active joint range of motion; ADL: Activity of daily living.

and the control group, VAS scores were significantly decreased more in the LBPP group than the control group (1.63 ± 0.52 in the LBPP group vs 2.60 ± 0.70 in the control group, P < 0.01).

The comparison results of gait spatial-temporal parameters are shown within-group (pre- vs post-treatment) or between two groups (LBPP vs control group) in Table 3 and Figure 4. No significant differences in stance phase, swing phase, mean velocity, cadence, stride length, step width, and knee flex-extension during walking at baseline (pre-treatment timepoint) between the two groups were noted. For comparisons within group between pre- and post-treatment, stance phase (%) in LBPP group was found increased significantly at the post-treatment timepoint (55.11 ± 3.13 vs 57.31 ± 2.39, P < 0.001), swing phase (%) in both groups were found decreased significantly at the post-treatment timepoint (LBPP group: 44.89 ± 3.13 vs 42.67 ± 2.39, P < 0.001; control group: 45.52 ± 3.35 vs 44.28 ± 2.60, P < 0.001), mean velocity (%height/s) in both groups were found increased significantly at the post-treatment timepoint (LBPP group: 57.64 ± 2.10 vs 64.28 ± 3.64, P < 0.001; control group: 57.72 ± 3.84 vs 59.33 ± 3.17, P < 0.001), cadence (steps/min) in LBPP group was found increased significantly at the post-treatment timepoint (106.76 ± 3.22 vs 110.10 ± 2.84, P = 0.002), stride length (m) in both groups were found increased significantly at the post-treatment timepoint (LBPP group: 0.46 ± 0.03 vs 0.50 ± 0.18, P < 0.001; control group: 0.47 ± 0.02 vs 0.48 ± 0.23, P = 0.025), and knee flex-extension (degrees) in LBPP group was found increased significantly at the post-treatment timepoint (66.14 ± 5.43 vs 72.34 ± 5.38, P = 0.004). For comparisons of post-treatment parameters among groups between LBPP group and control group, mean velocity was significantly increased more in LBPP group than
### Table 3 Comparison of spatiotemporal parameters within group (between pre- and post-treatment) and among groups (between lower body positive pressure group and control group)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LBPP group</th>
<th>Control group</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>$P$ value</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>$P$ value</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stance phase (%)</td>
<td>55.11 ± 3.13</td>
<td>54.49 ± 3.35</td>
<td>55.72 ± 2.60</td>
<td>57.31 ± 2.39</td>
<td>0.001</td>
<td>0.096</td>
<td>0.690</td>
<td>0.201</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swing phase (%)</td>
<td>44.89 ± 3.13</td>
<td>45.52 ± 3.35</td>
<td>44.28 ± 2.60</td>
<td>42.69 ± 2.39</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.690</td>
<td>0.197</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean velocity (%) (%height/s)</td>
<td>57.64 ± 2.10</td>
<td>57.72 ± 3.84</td>
<td>59.33 ± 3.17</td>
<td>64.28 ± 3.64</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.958</td>
<td>0.007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadence (steps/min)</td>
<td>106.76 ± 3.22</td>
<td>110.10 ± 2.84</td>
<td>104.46 ± 4.35</td>
<td>105.36 ± 3.58</td>
<td>0.002</td>
<td>0.141</td>
<td>0.233</td>
<td>0.008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stride length (m)</td>
<td>0.46 ± 0.03</td>
<td>0.47 ± 0.02</td>
<td>0.48 ± 0.23</td>
<td>0.50 ± 0.18</td>
<td>0.001</td>
<td>0.025</td>
<td>0.399</td>
<td>0.037</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step width (m)</td>
<td>0.15 ± 0.01</td>
<td>0.15 ± 0.01</td>
<td>0.15 ± 0.01</td>
<td>0.15 ± 0.01</td>
<td>0.080</td>
<td>0.343</td>
<td>0.753</td>
<td>0.854</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee flex-extension (Degree)</td>
<td>66.14 ± 5.43</td>
<td>72.34 ± 5.38</td>
<td>66.89 ± 5.33</td>
<td>66.40 ± 5.26</td>
<td>0.004</td>
<td>0.400</td>
<td>0.919</td>
<td>0.048</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Stands for comparison within lower body positive pressure (LBPP) group between pre-treatment and post-treatment.
2Stands for comparison within control group between pre-treatment and post-treatment.
3Stands for comparison among groups for pre-treatment between LBPP group and control group.
4Stands for comparison among groups for post-treatment between LBPP group and control group.

LBPP: Lower body positive pressure.

---

**Figure 2 Flow schematic of the study.** OA: Osteoarthritis; GZMU: Guangzhou Medical University; LBPP: Lower body positive pressure.

Control group (64.28 ± 3.64 in LBPP group vs 59.33 ± 3.17 in control group, $P = 0.007$), cadence was significantly increased more in LBPP group than control group (110.10 ± 2.84 in LBPP group vs 105.36 ± 3.58 in the control group, $P = 0.008$), stride length was significantly increased more in LBPP group than control group (0.50 ± 0.18 in LBPP group vs 0.48 ± 0.23 in control group, $P = 0.037$), and knee flex-extension was significantly increased more in LBPP group than control group (72.34 ± 5.38 in LBPP group vs 66.89 ± 5.33 in control group, $P = 0.048$).
DISCUSSION

Our study was designed as an RCT with the aim of studying an LBPP treadmill exercising training program for mild to moderate knee OA patients. We found patients in the LBPP group demonstrated more pain alleviation and improved walking ability after the intervention compared with patients in the conventionally treated group although both groups showed some improvement in clinical parameters (WOMAC, VAS, and knee active ROM) and gait parameters after their interventions. Moreover, more improvements in the LBPP group when compared with the control group with respect to walking speed, stride length, and knee ROM during walking represented improved walking ability. In addition, aquatic therapy research has proved the short-term benefits for patients with knee OA, but the high requirement of equipment limited the application.

Exercise improves the symptoms of knee OA, a finding which confirmed that pain relief was obtained with exercise[1]. However, due to the lack of relevant RCT-derived LBPP data in previous studies, it is difficult to determine whether the rehabilitative effects of LBPP for knee OA originate from the exercise effect itself or whether it has its own advantages over conventional exercise training. Thus, our study addresses this gap. In our RCT study, the LBPP group and groups both presented post-treatment improvements in WOMAC, VAS, and knee active ROM scores. Moreover, the LBPP group presented more advantages with respect to VAS relief when compared with the control group, which could be related to biomechanical changes caused by the weight support brought about by the LBPP positive pressure inflation chamber. In addition, the LBPP and control groups did not present improvements in ADL, which may be due to the “ceiling effect” of recruited patients in our study, that is to say, the knee OA patients included in this study had relatively high daily pre-treatment life activities.

The patients in both groups demonstrated improved gait function in mean velocity and stride length, whereas only the patients in the LBPP group demonstrated gait pattern changes after LBPP intervention (stance phase increased, and swing phase decreased). Previous studies presented the standing phase of affected side increased might be related to the pain released. Meanwhile, the LBPP treadmill proved useful for reducing pressure across the entire foot in normal subjects while running[21]. Previous
studies have also indicated that the effects of LBPP cause an increase in the reduction of the peak joint force on the knee joint[11]. Based on this finding, we have reason to infer that the knee pressure on the mechanical chain would be reduced accordingly, which might be crucial for knee OA patients undergoing rehabilitation.

The LBPP group also demonstrated an improvement in knee flex-extension during walking both within-group (pre-and post-treatment comparisons) and among the two groups (compared with the control group). Active knee ROM improvements might be more associated with stiffness and pain alleviation, which is also consistent with the clinical assessment findings in our study. Previous research has suggested that physical activity within a certain range most likely promotes the growth and maintenance of knee cartilage, ligaments, and bones in addition to strengthening muscles in order to appropriately distribute loads across the joint[22,23]. Meanwhile, the improvement in knee joint mobility might be related to the restoration of lower limb muscle strength after exercise[1]. Our previous study also found that after LBPP training, lower extremity muscle activity increased[10]. Increased muscle strength may cause a decrease in joint loading rates or localized stress in the articular cartilage, thereby playing an important role in pain reduction and physical function improvement of knee OA[8]. Although previous studies on aquatic therapy proved the
short-term benefits for patients with knee OA on the similar improved functional aspects, the high requirement of equipment limited the application.

Finally, we need to point out that all of the recruited patients in both groups were satisfied with the program and showed no side effects associated with the training program, which further supports the application of LBPP training in KOA rehabilitation from a clinical perspective. Our study results from the LBPP assistant intervention for knee OA patients may also reduce the burden of the physical therapist and increase cost-effectiveness than conventional training.

Limitations
There are several limitations to this RCT study. Our LBPP protocol was a 2-wk intensive inpatient training program focusing on the small sample size of inpatients due to health care policies in China, restrictions of the inclusion criteria (such as unilateral knee joint symptoms as the chief complaint and without the use of any painkillers during this study) and three-dimensional gait analysis application. Future studies should recruit more patients with the aim of observing the long-term effects of LBPP on knee OA and exploring changes at the anatomical level in addition to a personalized weight-support LBPP program for each patient.

CONCLUSION
The result of our RCT study showed that the LBPP group has a greater effect on improving gait parameters than the conventional group, although there was no significant advantage in clinical assessment. This finding indicates that LBPP treadmill exercise training could be considered an effective approach for alleviating pain symptoms and improving lower extremity locomotion in mild to moderate knee OA patients.

ARTICLE HIGHLIGHTS
Research background
Knee joint pain and stiffness are the two main symptoms of knee osteoarthritis (OA) and thus restrict a patient’s activities, such as walking and walking up and downstairs.

Research motivation
The lower body positive pressure (LBPP) treadmill as one of the emerging body weight support system devices brings new hope for exercise-related rehabilitation for knee OA patients.

Research objectives
The purpose of this study was to investigate the biomechanical effects and the subjective clinical assessment of LBPP treadmill walking exercise when compared with conventional therapy in mild to moderate knee OA patients.

Research methods
The eligible 18 knee OA patients were randomly assigned to two groups: LBPP and control groups. All patients underwent clinical assessments and three-dimensional gait analysis at pre- and 2-wk post-treatment.

Research results
The Western Ontario and McMaster Universities Arthritis Index and visual analog scale scores in both the LBPP group and control group were found to decrease significantly at the post-treatment point than the pre-treatment point. Moreover, compared with the control group, the LBPP group showed more improvements in walking speed, stride length, and knee range of motion during walking, which represented more improvement in walking ability.

Research conclusions
The results showed that the LBPP group has a greater effect on improving gait parameters than the conventional group, although there was no significant advantage in clinical assessment.
Research perspectives
This finding indicates that LBPP treadmill walking training might be an effective approach for alleviating pain symptoms and improving lower extremity locomotion in mild to moderate knee OA patients.

ACKNOWLEDGEMENTS
The author thanks graduate students Yi-Sha Liu, Shao-Ming Xu, Dong-Qin Huang, Pei-Xi Lian, and Yuan-Lu Zhang (Guangzhou Medical University) for data collection. The author also thanks Dr. Qiang Lin and Dr. Jun-Jie Liang for methodological guidance.

REFERENCES


16. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic


Effects of hypoxia on bone metabolism and anemia in patients with chronic kidney disease

Chao Kan, Xu Lu, Rui Zhang

ORCID number: Chao Kan 0000-0002-1348-1689; Xu Lu 0000-0002-6882-7667; Rui Zhang 0000-0003-4126-5972.

Author contributions: Zhang R initiated the project and gave constructive comments and suggestions for the manuscript; Kan C drafted the manuscript; Lu X provided assistance with the figures and tables; and all authors have read and approved the manuscript.

Conflict-of-interest statement: The authors declare that they have no competing interests to disclose.

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.

Country/Territory of origin: China

Specialty type: Urology and nephrology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Abstract

BACKGROUND
Abnormal bone metabolism and renal anemia seriously affect the prognosis of patients with chronic kidney disease (CKD). Existing studies have mostly addressed the pathogenesis and treatment of bone metabolism abnormality and anemia in patients with CKD, but few have evaluated their mutual connection. Administration of exogenous erythropoietin to CKD patients with anemia used to be the mainstay of therapeutic approaches; however, with the availability of hypoxia-inducible factor (HIF) stabilizers such as roxadustat, more therapeutic choices for renal anemia are expected in the future. However, the effects posed by the hypoxic environment on both CKD complications remain incompletely understood.

AIM
To summarize the relationship between renal anemia and abnormal bone metabolism, and to discuss the influence of hypoxia on bone metabolism.

METHODS
CNKI and PubMed searches were performed using the key words “chronic kidney disease,” “abnormal bone metabolism,” “anemia,” “hypoxia,” and “HIF” to identify relevant articles published in multiple languages and fields. Reference lists from identified articles were reviewed to extract additional pertinent articles. Then we retrieved the Abstract and Introduction and searched the results from the literature, classified the extracted information, and summarized important information. Finally, we made our own conclusions.

RESULTS
There is a bidirectional relationship between renal anemia and abnormal bone metabolism. Abnormal vitamin D metabolism and hyperparathyroidism can
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/License/s/by-nc/4.0/

Received: May 7, 2021
Peer review started: May 7, 2021
First decision: July 26, 2021
Revised: August 12, 2021
Accepted: October 25, 2021
Article in press: October 25, 2021
Published online: December 6, 2021
P-Reviewer: Vela D
S-Editor: Ma YJ
L-Editor: Wang TQ
P-Editor: Ma YJ

INTRODUCTION

Chronic kidney disease (CKD) is defined according to the presence of kidney damage or an estimated glomerular filtration rate lower than 60 mL/min per 1.73 m² for 3 mo or longer[1]. In addition to sustained kidney damage, patients with CKD are also at increased risk of developing multiple complications including renal anemia, abnormal mineral and bone metabolism, dyslipidemia, and malnutrition. The pathophysiology of anemia in CKD includes many important factors such as the presence of comorbidities, erythropoietin (EPO) deficiency resulting from lower nephron mass, the resistance of bone marrow to EPO action due to uremic toxins, a reduced red cell life span, hepcidin metabolism dysfunction, absolute and functional deficiency of iron, and an increase in proinflammatory mediators[2]. Abnormal bone metabolism in patients with CKD stems from disorders involving calcium and phosphorus metabolism, vitamin D deficiency, and elevated parathyroid hormone, leading to a higher risk of osteoporosis, myelofibrosis, and other bone diseases[3,4]. According to prior research and experience from clinical practice, the pathogenesis and potentially the treatment of renal anemia and abnormal bone metabolism may have many interactions[5]. For example, improving the hematopoietic microenvironment of bone marrow can be achieved by improving bone metabolism. When anemia is corrected, the oxygenation of bone tissues is expected to improve, leading to better bone function.

Hypoxia-inducible factor (HIF) is a heterodimeric transcriptional factor that can induce the production of EPO and oxygen-sensitive genes under the hypoxic environment. HIF-prolyl hydroxylase (HIF-PHD) is an enzyme that regulates the stability of the α subunit of HIF through post-translational HIF hydroxylation in an oxygen-
dependent manner, thereby maintaining the balance between environmental oxygen availability and HIF activities. Recent reports have confirmed the pivotal role of HIF-PHD as a critical gatekeeper overseeing the process of coordinated transcriptional adaptation to hypoxia and oxidative stress; its unique physiological position renders it a suitable therapeutic target for managing renal anemia. Inhibitors of HIF-PHD have been tested and validated as a viable therapeutic option clinically[6-8]. However, the hypoxic regulation of bone metabolism regarding bone maturation and osteoblast differentiation remains poorly understood, although hypoxia is expected to participate in the pathogenesis of both anemia and abnormal bone metabolism. There is still a lack of effective treatment options for the simultaneous occurrence of anemia and abnormal bone metabolism.

Therefore, the present study aimed to clarify the bidirectional relationship between anemia and abnormal bone metabolism, search for evidence that hypoxia can improve bone metabolism, and provide a new research direction for the treatment of complications in patients with CKD.

MATERIALS AND METHODS
CNKI and PubMed searches were performed using the key words “chronic kidney disease,” “abnormal bone metabolism,” “anemia,” “hypoxia,” and “HIF” to identify relevant articles published in multiple languages and fields. Reference lists from identified articles were reviewed to extract additional pertinent articles. Then we retrieved the Abstract and Introduction and searched the results from the literature, classified the extracted information, and summarized important information. Finally, we made our own conclusions. We have expanded the scope of literature search to reduce the risk of bias associated with article selection.

RESULTS
After reviewing 59 studies, we found that abnormal bone metabolism and renal bone disease were connected in the hematopoietic microenvironment. Abnormal vitamin D metabolism and hyperparathyroidism can affect bone metabolism, blood cell production, and survival rates through multiple pathways. Anemia will further attenuate the normal bone growth. According to the study of HIF in the treatment of renal anemia, HIF has more physiological potential. The hypoxic environment regulates bone morphogenetic protein, vascular endothelial growth factor, and neuropilin-1, and affects osteoblast/osteoclast maturation and differentiation through bone metabolic changes. Hypoxia preconditioning of mesenchymal stem cells (MSCs) can enhance their paracrine effects and promote fracture healing. Concurrently, hypoxia reduces the inhibitory effect on osteocyte differentiation by inhibiting the expression of fibroblast growth factor 23. Hypoxia potentially improves bone metabolism, but it still carries potential uncertainty, and the optimal concentration and duration of hypoxia remain unclear.

DISCUSSION

Relationship between abnormal bone metabolism and anemia in the pathogenesis of CKD
Effects of impaired vitamin D metabolism: Inorganic phosphorus within the fluid of cortical tubules increases significantly in patients with CKD, and this increase in phosphorus significantly inhibits the synthesis of 1,25(OH)2D3. The injured kidney is unable to synthesize calcitriol[3,4], and even if calcitriol is synthesized, osteoblastic vitamin D receptors (VDRs) cannot bind to it effectively[9-11]. These pathologic changes serve as triggers of abnormal bone metabolism observed in CKD patients. Furthermore, abnormal lipid metabolism associated with decreased vitamin D stores can aggravate CKD-related osteoporosis in patients with specific physical conditions [12]. In addition, the hematopoietic system, especially hematopoietic stem cells (HSCs) in the bone marrow (BM), are vulnerable to the adverse effects of CKD[13-17]. Bony disorders can damage the BM hematopoietic microenvironment. VDR is also expressed by immunocytes, and VDR activation on these cells enhances their anti-
inflammatory effects and also promotes the proliferation of erythrocyte progenitor cells[18,19]. During the course of CKD, the ability of VDRs to be activated is compromised, and their influence on erythrocyte progenitor cells is diminished. Inflammatory cytokines, which are released in higher quantities during CKD, also stimulate the liver to produce hepcidin[20,21], resulting in iron deficiency anemia. Earlier studies have confirmed that vitamin D is effective against abnormal bone metabolism in patients with CKD, and is widely used clinically. Icardi et al[22] showed that low hemoglobin (Hb) levels and EPO resistance in patients with CKD were associated with vitamin D deficiency. Along these lines, it is plausible that vitamin D supplementation in patients with CKD can ameliorate erythrocyte damage, increase Hb levels, and reduce EPO resistance, thereby improving symptoms related to anemia (Figure 1).

**Anemia and abnormal bone metabolism can be caused by secondary hyperparathyroidism:** With the increase of parathyroid hormone (PTH) during CKD, the generation of early erythroid progenitor cells is inhibited. PTH potentially antagonizes EPO production[23], increases the osmotic brittleness of erythrocytes, and impairs their survival[24]. In patients with CKD, elevated PTH causes accelerated bone turnover and is associated with myelofibrosis[25,26], which reduces the production of EPO and aggravates anemia. Moreover, due to the positive correlation between erythroferrone (ERFE) and EPO and lower endogenous EPO production, the inhibition of hepcidin mediated by ERFE is reduced, which also aggravates anemia[27]. Cinacalcet, a calcimimetic for treating secondary hyperparathyroidism (SHPT), has been shown to attenuate the inhibitory effects on erythrocytes posed by PTH[6,28,29], reduce the amount of EPO required for correcting anemia in patients with CKD[30], and improve bone integrity in such patients[31]. Cinacalcet can simultaneously optimize their BM hematopoietic microenvironment[32]. After parathyroidectomy (PTX), the required EPO dose in patients with CKD-related anemia significantly declines[33]. Together, these findings suggest that surgical or medical treatments directed toward SHPT and associated abnormal bone metabolism can potentially improve symptoms related to anemia (Figure 1).

**Abnormal bone metabolism can be exacerbated by anemia:** Due to the complications of abnormal calcium and phosphorus metabolism, patients with CKD frequently have osteodystrophy. Anemia will further attenuate the normal bone growth and affect the formation of bone marrow as well as the generation of hematopoietic stem cells. This constitutes a vicious circle.

**Effects of hypoxia on anemia and abnormal bone metabolism in patients with CKD**

Patients with CKD invariably suffer from a status of low tissue oxygen tension. Hypoxia is a common precipitator of abnormal bone metabolism and anemia. Because HIF-PHD inhibitors (HIF-PHI) have been used to treat renal anemia and abnormal bone metabolism interacts with anemia, it is possible that HIF-PHIs exert similar therapeutic efficacy against bone disease in patients with CKD. In the following sections, we will provide several unifying theories to support this therapeutic plausibility.

**Hypoxic environment and anemia:** Hypoxia may occur during episodes of microcirculatory insufficiency and hyperperfusion involving different tissues, including the kidney[34,35]. Studies have shown that the pathogenesis of CKD might include the loss of coherence within the microvascular network, resulting in an aberrantly heterogeneous pattern of focal microvascular rarefaction; this abnormality could diminish local blood flow velocity, relax vessel tone, and impair the oxygen uptake of tissues. From this perspective, tissue hypoxia is not uncommon during CKD[36,37]. Furthermore, chronic hypoxia by itself constitutes a vicious cycle, in which inflammatory cells are recruited and aggregate locally, promoting tissue fibrosis and further aggravating tissue hypoxia and organ damages[38,39]. On the other hand, anemia in patients with CKD is associated with destruction of the BM hematopoietic microenvironment. BM is widely considered to be a relatively hypoxic tissue[13], due to the finding that the low oxygen environment can optimize HSC activity[40,41] and improve anemia. The discovery of this hematopoiesis machinery facilitates the subsequent development of HIF-PHIs as a new treatment strategy for renal anemia. Under hypoxic conditions, the mechanisms by which treatment of renal anemia is accomplished predominantly involve the manipulation of HIF-α and PHD. HIF-2 regulates the expression of divalent metal transporter 1 (DMT1) and duodenal cytochrome b (Dcytb), thereby inhibiting the production of hepcidin in the liver. Dcytb has been shown to reduce dietary Fe$^{2+}$ to Fe$^{3+}$, which is transported by DMT1 later to small intestinal epithelial
cells for storage in the liver, small intestine, and macrophages. In addition, HIF-1 induces the expression of transferrin (Tf), transferrin receptor 1, and ferroportin (FPN), facilitating the transportation of iron stores to BM. HIFs also bind to the hypoxia responsive element within the promoter area of the EPO gene, and directly stimulate endogenous EPO production. Through the decrease of hepcidin, HIFs improve iron transportation and increase BM iron stores, resulting in anemia improvement. In the backdrop of this complicated scene, PHD is key to the regulation of the HIF pathway. During hypoxia, PHD2 is inactivated and HIF degradation is inhibited. In line with these findings, HIF-PHI has been shown to stabilize HIF-α and increase the expression of downstream targets.

The therapeutic advantage of HIF-PHI over conventional EPO for renal anemia lies in the fact that HIF-PHI is more physiologically directed relative to EPO.

Hypoxic environment and bone development: Hypoxia exhibits complex effects on bone metabolism. Heterotopic ossification (HO) refers to the formation of bone-like tissues outside the skeletal system, and the process of adaptation to a hypoxic microenvironment is a powerful driver for the development of HO. The hypoxic microenvironment increases the stability of HIF-1α, which regulates a coordinated network consisting of bone morphogenetic proteins, vascular endothelial growth factor, and neuropilin-1, all of which are implicated in the formation of ectopic bone-like tissues. Existing studies have found that the severity and duration of hypoxia to which tissues are exposed and the stage of osteoblast differentiation during which hypoxia occurs may influence bone growth and reconstruction.

In an environment of low oxygen level, pathways involved in bone metabolism are altered, which affect the maturation and differentiation of osteoblasts/osteoclasts. For osteoblasts, hypoxia predominantly occurs during their early stage of differentiation, and hypoxia facilitates premature osteoblast differentiation with incorrect signals produced for stimulating matrix maturation and mineralization. Through up-regulating HIF-1α, short-term hypoxia enhances matrix mineralization, promotes osteoblast differentiation and maturation, and accelerates osteogenesis. For osteoclasts, hypoxia increases osteoclast production irrespective of the differentiation stage during which hypoxia occurs, but the duration and severity of hypoxia may influence osteoclast differentiation. During hypoxia, anaerobic metabolism becomes predominant with acidic metabolites accumulation, causing mild acidosis of the local
microenvironment and driving the activation of osteoclasts. The regulatory relationship between HIF and adenosine A2B receptors in the hypoxic microenvironment can also enhance glycolysis and alter mitochondrial metabolism within osteoclasts, increasing the likelihood of bone absorption.

CKD patients with abnormal bone metabolism, especially those who are older, are at a higher risk of developing pathological fractures due to aberrant bone metabolism and the co-existing osteoporosis. Prior studies have demonstrated that hypoxic preconditioning of MSCs can enhance their paracrine effects by increasing the production of exosomal miR-126 through activating HIF-1α; hypoxia-treated exosomes promote bone fracture healing through exosomal miR-126.

FGF23 is mainly secreted by osteocytes. The bone-derived FGF23 acts in concert with PTH and active vitamin D calcitriol to regulate calcium and phosphate homeostasis. Overexpression of FGF23 inhibits osteoblast differentiation and bone matrix mineralization. Experimental studies have shown that in rat preosteoblasts, 1,25(OH)2-D-induced FGF23 expression is completely repressed under hypoxic conditions (0.2% O2) for 24 or 48 h, while hypoxia alone fails to trigger FGF23 expression. Therefore, hypoxia can reduce the inhibitory effect on osteocyte differentiation by inhibiting FGF23 expression. α-Klotho is also an important factor affecting bone metabolism. However, whether hypoxia affects bone metabolism by manipulating α-Klotho expression remains unclear.

Current guidelines for treating bone diseases fail to consider the control of hypoxia as a therapeutic option. Sustained and intermittent hypoxia may inhibit osteogenic differentiation and promote osteoclast function, and cyclic hypoxia has been proposed as a promising strategy for favorably affecting bone metabolism. Exposure to moderate oxygen concentration (> 2% in vitro and 9%–16% in vivo) persistently over days to weeks may increase bone mineralization potential, inhibit osteoclastic activity, and/or stimulate osteoblastic action. In fact, hypoxia may potentially improve bone metabolism, but the underlying side effects should not be neglected, including the induction of senescence involving bone marrow mesenchymal stem cells and the risk of bone metastases in patients with cancer. Additional research is necessary to discover and test the optimal regimen of cyclically exposing tissues to certain oxygen concentration and the time required for exposure (e.g., the duration, length, and frequency of exposures per day).

Delivering CKD progression reduces complications: Li et al. studied the stress response of renal tubules to hypoxia and found that during the transition from acute kidney injury to CKD, the absence of forkhead box O3 in renal tubules led to the deterioration of tubular structure and function, manifesting as a more severe CKD phenotype. In hypoxic kidneys, transcription factors associated with stress responses can be activated to ameliorate hypoxic injury and reduce the risk of progression to CKD.

Previous studies have shown that HIF-1 restricts the anabolic actions of PTH. In the bidirectional relationship between anemia and abnormal bone metabolism (Figure 1), lowering PTH can improve anemia and abnormal bone metabolism through multiple pathways. Although there is no clear evidence that HIF enhances vitamin D metabolism, HIF can act separately on several downstream pathways including calcitriol transformation, osteoblasts and osteoclasts growth and development, EPO production, and iron transport. Unfortunately, due to the limited evidence available, currently there is no therapeutic approach related to hypoxia for promoting bone metabolism. It is expected that potential HIF subtypes and pathways involved in the hematopoietic system and bone metabolisms will be discovered in the future.

CONCLUSION

This review summarizes findings from recent studies on renal anemia and abnormal bone metabolism in patients with CKD. Mounting evidence supports the notion that there is a connection between both CKD complications, ranging from their pathogenesis to viable therapeutic strategies. Several reports have shown that hypoxia can improve anemia and delay the progression of CKD, and hypoxia-targeted treatments such as HIF-PHIs are starting to be used clinically for anemia. Moreover, there is also evidence that hypoxia potentially improves bone metabolism, although the exact degree of low oxygen concentration and the duration required for obtaining results remain uncertain, necessitating further studies. Anemia and abnormal bone metabolism adversely influence patient prognosis. To improve the quality of life of patients with CKD, future studies should address the effect of HIF on bone metabolism while...
treating anemia, and HIF may be a useful treatment for improving the prognosis of patients with CKD.

**ARTICLE HIGHLIGHTS**

**Research background**
Abnormal bone metabolism and renal anemia seriously affect the prognosis of patients with chronic kidney disease (CKD). Currently, there are few studies on the evaluation of their mutual connection. With the availability of hypoxia-inducible factor (HIF) stabilizers, more therapeutic choices for renal anemia are expected in the future. However, the effects posed by the hypoxic environment on abnormal bone metabolism remain incompletely understood. If we can find evidence that HIF could improve both complications, it will be a great advantage to improve the prognosis of patients with CKD.

**Research motivation**
The purpose of this article is to summarize the relationship between renal anemia and abnormal bone metabolism, and to discuss the influence of hypoxia on bone metabolism, in order to provide a new way of thinking for the future studies on the treatment of CKD complications.

**Research objectives**
To clarify the bidirectional relationship between anemia and abnormal bone metabolism, to find evidence that hypoxia can improve bone metabolism, and to provide a new research direction for the treatment of complications in patients with CKD.

**Research methods**
We searched relevant articles published in multiple languages and fields, summarized important information, and drew our conclusions.

**Research results**
Anemia and bone metabolism interact. The hypoxic environment could affect osteoblast/osteoclast maturation and differentiation, enhance the paracrine effect of mesenchymal stem cells, and reduce the inhibitory effect of fibroblast growth factor 23 on osteocyte differentiation. Hypoxia potentially improves bone metabolism, but the optimal concentration and duration of hypoxia remain unclear and need further study.

**Research conclusions**
There is a bidirectional relationship between renal anemia and abnormal bone metabolism. The relationship has rarely been studied. Hypoxia may improve bone metabolism, but the concentration and duration of hypoxia remain unclear and need further study. To improve the quality of life of patients with CKD, future studies should address the effect of HIF on bone metabolism while treating anemia, and HIF may be a useful treatment for improving the prognosis of patients with CKD.

**Research perspectives**
In future studies, we can focus more on the exact degree of hypoxia concentration and duration required for improving bone metabolism.

**REFERENCES**


5. Tanaka M, Komaha H, Fukagawa M. Emerging Association Between Parathyroid Hormone and


Kan C et al. Effects of hypoxia on bone metabolism and anemia


51 Bruegge K, Jelkmann W, Metzen E. Hydroxylation of hypoxia-inducible transcription factors and chemical compounds targeting the HIF-alpha hydroxylases. Curr Med Chem 2007; 14: 1853-1862


59 Frey JL, Stokpo DP, Faugere MC, Riddle RC. Hypoxia-inducible factor-1α restricts the anabolic actions of parathyroid hormone. *Bone Res* 2014; 2: 14005 [PMID: 26273518 DOI: 10.1038/boneres.2014.5]
Intracuff alkalinized lidocaine to prevent postoperative airway complications: A meta-analysis

Zhen-Xing Chen, Zhou Shi, Bin Wang, Ye Zhang

ORCID number: Zhen-Xing Chen 0000-0002-3213-0497; Zhou Shi 0000-0001-5850-8462; Bin Wang 0000-0002-1177-2597; Ye Zhang 0000-0002-0627-7057.

Author contributions: Chen ZX, Wang B and Zhang Y participated in the design; Chen ZX and Shi Z extracted the data; Chen ZX, Wang B and Shi Z performed the quality assessment; Chen ZX performed the statistical analysis; Zhang Y wrote the manuscript.

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

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.

Country/Territory of origin: China

Specialty type: Anesthesiology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report’s scientific quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0

Zhen-Xing Chen, Zhou Shi, Bin Wang, Department of Anesthesiology and Perioperative Medicine, The Second Affiliated Hospital of Anhui Medical University, Hefei 230601, Anhui Province, China

Ye Zhang, Department of Anesthesiology, The Second Affiliated Hospital of Anhui Medical University, Hefei 230601, Anhui Province, China

Corresponding author: Ye Zhang, PhD, Doctor, Full Professor, Department of Anesthesiology, The Second Affiliated Hospital of Anhui Medical University, No. 678 Furong Road, Hefei 230601, Anhui Province, China. zhangye_hassan@sina.com

Abstract

BACKGROUND
Post-extubation cough is a common phenomenon in surgical patients undergoing general anesthesia, which can lead to potentially dangerous complications. In this meta-analysis, we evaluated the efficacy and safety of intracuff alkalinized lidocaine in patients with tracheal intubation to prevent cough and other airway complications during the perioperative period.

AIM
To perform a systematic review and meta-analysis of intracuff alkalinized lidocaine for the prevention of postoperative airway complications.

METHODS
PubMed, Embase, Cochrane, and Web of Science were searched for randomized controlled trials (RCTs) that compared intracuff alkalinized lidocaine to placebo. We used risk-of-bias assessment to assess the RCTs, and the quality of evidence was assessed using the grading of recommendations, assessment, development, and evaluations.

RESULTS
Twelve randomized trials (1175 patients) were analyzed. Meta-analysis showed that intracuff alkalinized lidocaine was associated with less cough compared to that produced by placebo [risk ratio (RR): 0.38; 95% confidence interval (CI): 0.23-0.63]. Similarly, intracuff alkalinized lidocaine was more effective than the control in reducing postoperative sore throat at 24 h (RR: 0.19; 95% CI: 0.09-0.41) and postoperative hoarseness (RR: 0.38; 95% CI: 0.21-0.69).

CONCLUSION
Intracuff alkalinized lidocaine is an effective adjuvant that can decrease airway complications, such as coughing, hoarseness, and sore throat.

Key Words: Cough; Hoarseness; Lidocaine; Sore throat; Airway complication; Intracuff; Meta-analysis

Core Tip: Our study is different to previous systematic reviews and meta-analysis. We focused on adult patients and included relevant literature on alkalinized lidocaine in the analysis. In addition, this is the first systematic review and meta-analysis to analyze lubrication of the cuff before intubation in order to eliminate the influence of confounding factors on the results.

INTRODUCTION
Tracheal intubation is the most commonly used airway management method in general anesthesia. Due to its high safety, simple operation, and convenient management, it has become the most important airway management method in most operations[1]. However, this approach has been associated with some problems, such as postoperative airway complications[2], which are common phenomena and adverse reactions in patients who underwent elective general anesthesia. Under normal physiological conditions, cough serves as a protective mechanism, which can clear sputum and foreign matter from the airway and prevent aspiration that may cause pneumonia[3]. However, after the operation, during recovery from general anesthesia, coughing may cause potentially dangerous complications[4]. Coughing may lead to increased intracranial pressure[5,6], which may cause re-bleeding after the evacuation of intracranial hematoma and even lead to brain hernia. High blood pressure induced by cough can also result in the risk of cerebral hemorrhage and bleeding from surgical wounds. Furthermore, cough itself may also cause severe complications such as tracheospasm and bronchospasm[7]. Also, sore throat[8] and hoarseness[9] are common adverse events after general anesthesia. Although pharyngeal pain and hoarseness are mostly mild and self-limited, they may result in strong adverse emotional experiences in patients, reduce patients’ satisfaction with the surgical process, and ultimately result in a poor medical experience. To reduce the occurrence of postoperative airway-related complications, many interventions have been proposed, such as intravenous injection of fentanyl, remifentanil, dextromethophyrimidine[10], and other drugs[11], extubation under deep anesthesia[12], local application of local anesthetics[13,14], filling of lidocaine in the tracheal catheter cuff[15-17], intratracheal administration of lidocaine[18], intravenous injection of lidocaine[19-21] and so on. Among these, intracuff lidocaine can be used as local anesthesia, to reduce complications during extubation, and to avoid the side effects of lidocaine on the circulation and central nervous system during general application. Nevertheless, lidocaine is not easy to diffuse in the cuff, and adding sodium bicarbonate can greatly enhance the diffusion ability of lidocaine, so as to achieve better action on the tracheal mucosa[22]. Therefore, it is necessary to perform a systematic review and meta-analysis to summarize the efficacy of intracuff alkalinized lidocaine in the prevention of postoperative airway-related complications.
We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for the reporting of meta-analyses of randomized controlled trials (RCTs)\textsuperscript{[23]}. The protocol was registered in the International Prospective Register of Systematic Reviews (trial registration number: CRD42020178143).

**Search strategy**
A comprehensive literature search of PubMed (until May 2020), Embase (until May 2020), Cochrane (until May 2020), and Web of Science (until May 2020) was performed. We used a combination of free text and database-specific subjects (i.e., MESH or EMTREE headings) to describe ‘lidocaine’. The search strategy is shown in Supplementary material: Appendix A. No language restrictions were placed on inclusion. Non-English studies were translated using online translation. Finally, the references of all articles retrieved from the search were manually scrutinized for any relevant trials not identified using the strategy described above.

**Inclusion and exclusion criteria**
Studies were selected if they were: (1) Conducted as an RCT; (2) Compared intracuff alkalinized lidocaine fills with a control (i.e., with air or saline fills) in patients ≥ 18 years old who received tracheal intubation under general anesthesia; and (3) Reported the incidence of cough, hoarseness, sore throat and/or visual analogue scale (VAS) of sore throat, among other outcomes. Selected studies were then excluded if they met one or more of the following criteria: (1) The trial included emergency surgery; (2) It was a small-scale preliminary pilot study; (3) The necessary data could not be extracted or calculated from the published results; (4) Other lidocaine administration methods were included in the experimental group; and (5) There were other intervention measures in the experimental group.

**Outcomes**
The primary outcome was the incidence of post-extubation cough. Secondary outcomes included the following: Incidence of postoperative hoarseness, the incidence of a postoperative sore throat within 24 h, VAS of a postoperative sore throat at 1 h and 24 h.

**Screening and data extraction**
Two independent reviewers (Chen ZX and Shi Z) screened the retrieved titles and abstracts for potential inclusion, reviewed the full text of potential studies, and extracted the data from studies that met the inclusion criteria. Any discrepancies between the reviewers were resolved through a consensus process. When the two reviewers failed to reach an agreement, the final decision was made by the third reviewer (Wang B). Data extraction was completed by two coauthors (Chen ZX and Shi Z) using a predesigned piloted data extraction form. The data extraction form collected information regarding the year of publication; primary author; country of origin; types of surgery; participant characteristics (gender, age, number, inclusion and exclusion criteria); intervention; lidocaine and placebo group events; severity of postoperative sore throat. Dichotomous data were converted to incidences for data synthesis, and continuous data were recorded using mean ± SD. Any disagreement was resolved through the consensus process discussed previously.

**Assessment risk of bias**
The risk of bias was assessed in duplicate using the method outlined in the Cochrane Risk of Bias Tool for Non-Randomized Studies. The risk of bias was assessed as low, moderate, high, for each selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Any disagreement was resolved by consensus.

**Statistical analysis**
The meta-analysis was performed using RevMan 5.3 software (Cochrane Collaboration, Oxford, England). The level of evidence quality of each study was estimated according to the guidelines of the grading of recommendations, assessment, development, and evaluation (GRADE). We examined the following five categories: Risk of bias, consistency, directness, imprecision, and reporting bias. RCTs began as high-quality evidence and were rated down based on the described criteria. The evidence grades were classified as high quality (further research is unlikely to change the confidence in the estimate of effect), moderate quality (further research is likely to
have an important impact on our confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low quality (we are very uncertain about the estimate).

If necessary, standard deviations from the confidence interval (CI) limits, the standard error, or the range values provided in the past studies were estimated. The effect sizes of dichotomous outcomes were reported as risk ratios (RR), and the mean difference (MD) was reported for continuous outcomes.

Heterogeneity was assessed using the Cochrane Q test and I² statistic. I² = 50% was considered low heterogeneity, I² = 50% to 75% as moderate, and I² = 75% to 100% as high. P values < 0.05 were considered statistically significant. A fixed-effect model was used if heterogeneity was considered low. If P statistic ≥ 50% and P < 0.05, a random-effects model was applied to the data. The statistical methods of this study were reviewed by Peng Z from the Department of Maternal, Child, and Adolescent Health, School of Public Health, Anhui Medical University, Hefei, China.

A sensitivity analysis was performed to assess the potential influence in our analysis. We attempted to exclude RCTs with: (1) A high risk of bias; (2) Only female subjects; and (3) Cuff prefilling.

RESULTS

Study selection
A total of 580 articles were identified from the primary electronic databases (PubMed: 188, Embase: 194, Cochrane: 109, Web of Science: 89. After removing duplicates, we screened 416 studies based on the abstracts, among which 62 full-text articles were assessed for eligibility. Finally, 12 studies were included in the analysis (Figure 1).

Study characteristics/participants
The 12 included studies involved a total of 1175 participants with an average age ranging from 36.71 years to 52.00 years, and gender ratios ranging from 0-1.96. All studies were RCTs with placebo or no treatment control arms. Seven trials included patients with an ASA status of I and II[24-30]. Five trials included patients with an ASA status of I, II, and III[31-35]. The included surgeries were: One gynecological surgery[30]; two lumbar surgeries[33,34]; one orthopedic, spine and general surgery[25]; one gynecological, orthopedic, or plastic surgery[26]; one gynecological or plastic surgery[28]; one thyroidectomy surgery[29]. Four studies did not report the type of surgery[24,27,32,35]. Opioids were used in all studies except one which did not report on the use of anesthetics[24]. Saline and air were used in the control group in three and seven experiments[24,25,28,29,33-35], respectively. Two experiments used both saline and air[27,31]. One of the experiments using air in the control group also used 1.4%NaHCO₃ as an intervention[29]. In addition, 5 studies lubricated the cuff of the tracheal tube with sterile water or water-soluble gel or normal saline spray before intubation[26,29,30,33,34], and 2 studies performed prefilled at least 90 min before tracheal intubation[32,35] (Table 1).

Risk-of-bias and GRADE assessment
Six trials were judged to be a low risk of bias in all domains. Six trials had an unclear risk of bias, mostly related to random sequence generation and allocation concealment. Two trials had a high risk of bias. The domain that was judged to have a high risk of bias was performance bias and detection bias (Figure 2). The GRADE assessment demonstrated an overall high quality of evidence for the incidence of post-extubation cough and hoarseness. The quality of evidence for the following outcomes was considered moderate: incidence of a postoperative sore throat at 24 h, VAS of a postoperative sore throat at 1 h and 24 h (Supplementary material: Appendix B).

Incidence of post-extubation cough
The aggregate effect of the 7 studies (n = 629) evaluating the effect of intracuff alkalinized lidocaine on the incidence of post-extubation cough was in favor of lidocaine over the control (RR: 0.38; 95%CI: 0.23-0.63). Subgroup analysis revealed that the use of intracuff alkalinized lidocaine could also result in a large reduction in post-extubation cough regardless of the lubricated cuff. Concerning subgroup analysis, a significant effect in the reduction of the post-extubation cough was found in the lubricated group (RR: 0.30; 95%CI: 0.13, 0.68) compared with the non-lubricated group.
Table 1 Characteristics of the included trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Country</th>
<th>Age (yr)</th>
<th>Male/ Female</th>
<th>Sample size</th>
<th>ASA status</th>
<th>Surgery</th>
<th>Intervention/comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rizvanović et al [31], 2019</td>
<td>Bosnia and Herzegovina</td>
<td>49.4 (18-65)</td>
<td>44/46</td>
<td>90</td>
<td>I, II, III</td>
<td>Elective surgery</td>
<td>1 Alkalinized 2% lidocaine; 2 0.9% saline; 3 Air</td>
<td>IPOST</td>
</tr>
<tr>
<td>Nath et al [32], 2018</td>
<td>USA</td>
<td>52 (18-80)</td>
<td>73/127</td>
<td>200</td>
<td>I, II, III</td>
<td>NR</td>
<td>1 Alkalinized 2% lidocaine; 2 0.9% saline</td>
<td>IPC</td>
</tr>
<tr>
<td>Gaur et al [24], 2017</td>
<td>India</td>
<td>44.62 (18-65)</td>
<td>51/49</td>
<td>100</td>
<td>I, II</td>
<td>NR</td>
<td>1 Alkalinized 2% lidocaine; 2 Air</td>
<td>IPOST</td>
</tr>
<tr>
<td>Suma et al [25], 2015</td>
<td>Brazil</td>
<td>NR (≥ 18)</td>
<td>13/37</td>
<td>50</td>
<td>I, II</td>
<td>Elective surgery</td>
<td>1 Alkalinized 4% lidocaine; 2 0.9% saline</td>
<td>IPC, IPOST</td>
</tr>
<tr>
<td>Navarro et al [36], 2012</td>
<td>Brazil</td>
<td>36.71 (18-60)</td>
<td>51/99</td>
<td>150</td>
<td>I, II</td>
<td>NR</td>
<td>1 Alkalinized 2% lidocaine; 2 0.9% saline 3 Air</td>
<td>IPC, IPH</td>
</tr>
<tr>
<td>Navarro et al [37], 2007</td>
<td>Brazil</td>
<td>45.15 (18-65)</td>
<td>NR</td>
<td>50</td>
<td>I, II</td>
<td>Gynecological surgery or plastic surgery</td>
<td>1 Alkalinized 2% lidocaine; 2 Air</td>
<td>IPOST</td>
</tr>
<tr>
<td>Estebe et al [29], 2005</td>
<td>USA</td>
<td>47.67 (≥ 18)</td>
<td>13/47</td>
<td>60</td>
<td>I, II</td>
<td>Thyroidectomy surgery</td>
<td>1 Alkalinized 2% lidocaine (8.4%NaHCO₃); 2 Alkalinized 2% lidocaine (1.4%NaHCO₃); 3 Air</td>
<td>IPC, IPH, VAS of POST</td>
</tr>
<tr>
<td>Estebe et al [33], 2004</td>
<td>USA</td>
<td>49.67 (≥ 18)</td>
<td>39/21</td>
<td>60</td>
<td>I, II, III</td>
<td>Lumbar spinal surgery</td>
<td>1 Alkalinized 2% lidocaine (lubricated with sterile water); 2 Alkalinized 2% lidocaine (lubricated with water-soluble gel); 3 Air</td>
<td>IPC, IPH, VAS of POST</td>
</tr>
<tr>
<td>Estebe et al [34], 2002</td>
<td>USA</td>
<td>46.5 (≥ 18)</td>
<td>27/23</td>
<td>50</td>
<td>I, II, III</td>
<td>Lumbar spinal surgery</td>
<td>1 Alkalinized 2% lidocaine; 2 2% Lidocaine; 3 Air</td>
<td>IPC, IPH, VAS of POST</td>
</tr>
<tr>
<td>Navarro et al [35], 1997</td>
<td>USA</td>
<td>40.15 (NR)</td>
<td>18/88</td>
<td>106</td>
<td>I, II, III</td>
<td>NR</td>
<td>1 Alkalinized 2% Lidocaine; 2 Air</td>
<td>IPOST, VAS of POST</td>
</tr>
<tr>
<td>D’Aragon et al [36], 2013</td>
<td>Canada</td>
<td>41.8 (≥ 18)</td>
<td>0/59</td>
<td>59</td>
<td>I, II</td>
<td>Elective gynecological surgery</td>
<td>1 Alkalinized 2% lidocaine; 2 0.9% saline</td>
<td>IPC</td>
</tr>
</tbody>
</table>


(RR: 0.53; 95% CI: 0.37-0.75). However, there was no subgroup difference in relation to lubrication of the cuff (P = 0.21) (Figure 3).

**Incidence of postoperative hoarseness**

Based on the data pooled from 5 trials (n = 370), the use of intracuff alkalinized lidocaine demonstrated a large reduction in postoperative hoarseness (RR: 0.38; 95% CI: 0.21-0.69) (Figure 4).

**Incidence of a postoperative sore throat within 24 h**

The data from four trials (n = 290) indicated that intracuff alkalinized lidocaine reduced the incidence of a postoperative sore throat within 24 h (RR: 0.19; 95% CI: 0.09-0.41) (Figure 5).

**VAS of a postoperative sore throat at 1 h and 24 h**

Five trials that included 476 participants demonstrated a large reduction in the VAS of a postoperative sore throat at 1 h with the use of intracuff alkalinized lidocaine (MD: -18.30; 95% CI: -22.79, -13.82) (Figure 6). Similarly, in the 5 studies (n = 476) that evaluated intracuff alkalinized lidocaine on the VAS of a postoperative sore throat at 24 h, a significant benefit of alkalinized lidocaine compared with the control was identified (MD: -14.86; 95% CI: -15.75, -13.98) (Figure 7).
Figure 1 Flow diagram of included and excluded studies. RCT: Randomized controlled trial.

Figure 2 Risk of bias assessment for the primary studies.

Assessment of publication bias
The funnel plot for the included studies showed an asymmetrical characteristic, which suggested a possible publication bias (Figure 8).
DISCUSSION

In this study, 12 RCTs on the prevention of postoperative airway complications with intracuff alkalinized lidocaine were included. This meta-analysis showed that intracuff alkalinized lidocaine could significantly reduce the incidence of post-extubation cough with high quality of evidence, compared with the control group, and many surgical patients may benefit from the application of intracuff alkalinized lidocaine in clinical practice. At the same time, subgroup analysis showed that saline lubrication before intubation reduced the incidence of post-extubation cough; nonetheless, the observed differences were not statistically significant. Therefore, the evidence in this study
strongly suggests that intracuff alkalinized lidocaine can prevent post-extubation cough, and further study is unlikely to change this conclusion. Regarding the VAS of a postoperative sore throat at 1 h and 24 h, intracuff alkalinized lidocaine reduced the severity of postoperative sore throat at 1 h or 24 h. Similarly, the use of intracuff alkalinized lidocaine demonstrated a large reduction in postoperative hoarseness.

In terms of safety, there is no doubt that the usage of intracuff alkalinized lidocaine is much safer than the usage of intravenous lidocaine. In terms of the extubation time, no study has shown that intracuff alkalinized lidocaine may prolong the extubation

---

**Figure 6** Forrest plots showing the effects of the intervention. Visual analogue scale of a postoperative sore throat at 1 h. CI: Confidence interval; SD: Standard deviation.

**Figure 7** Forrest plots showing the effects of the intervention. Visual analogue scale of a postoperative sore throat at 24 h. CI: Confidence interval; SD: Standard deviation.

**Figure 8** Funnel plot for evaluation of potential publication bias. RR: Risk ratio.
Table 2 Sensitivity analyses: The effect of potential biases on primary and secondary outcomes

<table>
<thead>
<tr>
<th>Potential bias or limitations excluded</th>
<th>IPC RR (95% CI), I</th>
<th>IPH RR (95% CI), I</th>
<th>IPOST within 24 h RR (95% CI), I</th>
<th>VAS of POST at 1 h RR (95% CI), I</th>
<th>VAS of POST at 24 h RR (95% CI), I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.38 (0.23, 0.63), 82%</td>
<td>0.38 (0.21, 0.69), 74%</td>
<td>0.19 (0.09, 0.41), 0%</td>
<td>-18.30 (-22.79, -13.82), 73%</td>
<td>-14.86 (-15.75, -13.98), 43%</td>
</tr>
<tr>
<td>Only females</td>
<td>0.33 (0.20, 0.52), 69%</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Cuff prefilling</td>
<td>0.35 (0.19, 0.63), 85%</td>
<td>NE</td>
<td>NE</td>
<td>-17.59 (-18.69, -16.49), 77%</td>
<td>-14.81 (-17.22, -12.41), 54%</td>
</tr>
<tr>
<td>A high risk of bias</td>
<td>NE</td>
<td>NE</td>
<td>0.19 (0.08, 0.48), 0%</td>
<td>-18.45 (-25.61, -11.29), 77%</td>
<td>-14.37 (-18.31, -10.43), 56%</td>
</tr>
</tbody>
</table>


Our results revealed that intracuff alkalinized lidocaine decreased postoperative airway complications. To achieve a significant therapeutic effect, large doses of lidocaine may be necessary without alkalinization[37]. According to Estebe et al[34], plasma lidocaine levels confirmed the increased diffusion of lidocaine through the cuff when lidocaine was alkalinized. Moreover, this increased diffusion did not lead to vocal cord palsy. Therefore, the use of a small dose of alkalinized lidocaine (40 mg) is a relatively easy and safe practice that avoids the use of large doses of lidocaine.

The main limitation and disadvantage of this study is the obvious heterogeneity, although a pre-defined subgroup analysis was performed. Clinically, opioids, inhalational anesthetics, and the depth of anesthesia during extubation may have an impact on cough, hoarseness, and sore throat after extubation. In order to minimize these possible confounding factors, we conducted a special sensitivity analysis. Meta-analysis still showed the effectiveness of intracuff alkalinized lidocaine when we excluded RCTs with: (1) A high risk of bias; (2) Only female subjects; (3) Cuff prefilling (Table 2). However, there are still many variables, such as operation time, inflation volume of the tracheal catheter cuff, anesthesiologist’s expertise and ability, which were not systematically reported in the selected studies, thus cannot be analyzed. In addition, only 7 studies with primary outcome were eligible for inclusion, and the funnel plot results are not accurate. To sum up, the use of intracuff alkalinized lidocaine after tracheal intubation is a simple, economical and safe choice to prevent postoperative cough, sore throat, and hoarseness in adult patients. Anesthesiologists can use this technique in clinical patients.
CONCLUSION

This meta-analysis revealed that intracuff alkalinized lidocaine decreased postoperative airway complications, including coughing, hoarseness, and sore throat. Furthermore, for patients with a post-extubation sore throat, it could also reduce the degree of pain.

ARTICLE HIGHLIGHTS

Research background
Tracheal intubation is the most commonly used airway management method in general anesthesia. However, this approach has been associated with some problems, such as postoperative airway complications, which are common phenomena and adverse reactions in patients who underwent elective general anesthesia. To reduce the occurrence of postoperative airway-related complications, many interventions have been proposed. Among these, intracuff alkalinized lidocaine can be used as local anesthesia, to reduce complications during extubation, and to avoid the side effects of lidocaine on the circulation and central nervous system during general application.

Research motivation
Intracuff lidocaine can be used as local anesthesia, to reduce complications during extubation, and to avoid the side effects of lidocaine on the circulation and central nervous system during general application. Nevertheless, lidocaine is not easy to diffuse in the cuff, and adding sodium bicarbonate can greatly enhance the diffusion ability of lidocaine, to achieve better action on the tracheal mucosa.

Research objectives
Perform a systematic review and meta-analysis to summarize the efficacy of intracuff alkalinized lidocaine in the prevention of postoperative airway-related complications.

Research methods
A comprehensive literature search of Pubmed (until May 2020), Embase (until May 2020), Cochrane (until May 2020), and Web of Science (until May 2020) was performed. Heterogeneity was assessed using the Cochrane test and statistic. A fixed-effect model was used if heterogeneity was considered low. If statistic ≥ 50% and P < 0.05, a random-effects model was applied to the data.

Research results
Twelve randomized trials (1175 patients) met the inclusion criteria. The meta-analysis showed that intracuff alkalinized lidocaine was associated with less cough compared to that produced by placebo. Similarly, intracuff alkalinized lidocaine was more effective than the control in reducing postoperative sore throat at 24 h and postoperative hoarseness. Five trials that included 476 participants demonstrated a large reduction in the visual analogue scale of a postoperative sore throat at 1 h or 24 h with the use of intracuff alkalinized lidocaine.

Research conclusions
Intracuff alkalinized lidocaine decreased postoperative airway complications, including coughing, hoarseness, and sore throat. Furthermore, for patients with a post-extubation sore throat, it could also reduce the degree of pain.

Research perspectives
The use of intracuff alkalinized lidocaine after tracheal intubation is a simple, economical and safe choice to prevent postoperative cough, sore throat, and hoarseness in adult patients. Anesthesiologists can use this technique in clinical patients.

REFERENCES

Chen ZX et al. A meta-analysis for lidocaine


Rarely fast progressive memory loss diagnosed as Creutzfeldt-Jakob disease: A case report

Yong-Wei Xu, Jie-Qun Wang, Wei Zhang, Shu-Chang Xu, Yun-Xia Li

ORCID number: Yong-Wei Xu 0000-0002-7416-4281; Jie-Qun Wang 0000-0002-5905-3313; Wei Zhang 0000-0003-4970-2073; Shu-Chang Xu 0000-0002-4841-462X; Yun-Xia Li 0000-0002-0626-2584

Author contributions: Xu YW wrote the initial draft of the manuscript; Xu YW, Wang JQ and Zhang W contributed to data acquisition and analysis; Li YX and Xu SC contributed to revision of the 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: No potential conflicts of interest relevant to this article were reported.

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).

Supported by: Shanghai Shenkang Hospital Development Center, No. SHDC12016109.

Country/Territory of origin: China

Specialty type: Neurosciences

Abstract

BACKGROUND
Creutzfeldt-Jakob disease (CJD) is a rare degenerative disease of the central nervous system that can be contagious or hereditary and is a rare cause of rapidly progressive dementia. It almost always results in death within 1-2 years from symptom onset.

CASE SUMMARY
Here, we report the case of a 57-year-old male who initially experienced dizziness followed by a 1-mo fast decline in memory function. He presented to the local hospital and underwent magnetic resonance imaging and cerebrospinal fluid (CSF) examination, with no definitive diagnosis. However, the symptoms of progressive forgetting worsened. In addition, he exhibited progressive involuntary tremor of the limbs. Then, he came to our hospital, and according to the results of CSF examination, electroencephalography (EEG) and magnetic resonance imaging (MRI) tests and clinical manifestations of cerebellar ataxia, dementia, and myoclonus that rapidly progressed, with a short duration of illness, he was finally diagnosed with sporadic CJD (sCJD).

CONCLUSION
This case report aims to create awareness among physicians to emphasize auxiliary examination, CSF examination, EEG and MRI tests and recognition of cerebellar ataxia, dementia, and myoclonus that rapidly progress to prompt pursuit of an early diagnosis and identification of sCJD and to reduce complications.

Key Words: Creutzfeldt-Jakob disease; Prion disorders; Progressive memory loss; Dementia; Case report
Core Tip: Creutzfeldt-Jakob disease (CJD) is a rare degenerative disease of the central nervous system that can be contagious or hereditary and is a rare cause of rapidly progressive dementia. Here, we report the case of a 57-year-old male who initially experienced dizziness followed by a 1-mo fast decline in memory function. According to the cerebrospinal fluid examination, electroencephalography, and, magnetic resonance imaging tests and cerebellar ataxia, dementia, and myoclonus that rapidly progressed, with a short duration of illness Clinical manifestations then he was finally diagnosed with sporadic CJD (sCJD). This case reports aim to create awareness amongst physicians to emphasize the importance of pursuing an early diagnosis and identifying sCJD and reducing complications.

URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10638.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10638

INTRODUCTION
Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disorder and the most common prion disease in humans; it is characterized by severe nervous system damage and high mortality\[1\]. The prion hypothesis proposed by Prusiner in 1982 is now widely accepted, by which CJD pathogenesis involves the conversion of normal cellular prion protein (PrP) to pathogenic forms\[2\]. The mechanism for triggering this conformational change is unknown, but abnormal PrP leads to neuronal degeneration, astrocytic gliosis, and spongiform changes, accompanied by rapid cognitive decline and death\[3\]. Four types of CJD are known thus far: sporadic, genetic/familial, iatrogenic, and variant\[4\]. Sporadic CJD (sCJD) cases account for ~85% of CJD and are considered among the most fatal neurological disorders\[5\]. The characteristic clinical picture of CJD is rapidly progressive dementia accompanied by behavioral disturbances, ataxia, and myoclonus\[6\]. Here, we report a case of sCJD with progressive memory loss. The aim is to enrich the clinical data and to provide a reference for improving the diagnosis and prognosis of this disease. At the same time, clinicians will be better informed about typical CJD.

CASE PRESENTATION

Chief complaints
A month prior to admission to our hospital, a 57-year-old man was admitted to the local hospital with dizziness, obvious memory loss, and rapidly progressive dementia.

History of present illness
A month prior to admission to our hospital, a 57-year-old man was admitted to the local hospital with dizziness, obvious memory loss, and rapidly progressive dementia.

History of past illness
The patient underwent magnetic resonance imaging (MRI) that showed an abnormality in the head of the right caudate nucleus suggesting multiple lacunar infarctions.

Personal and family history
Denial the family history of infectious diseases.

Physical examination
The patient was admitted to our department following 1 mo of progressive memory...
loss accompanied by disturbed consciousness, dementia, depression, and inability to answer questions or complete physical examinations. Based on the reports of the patient’s family and a review of records, the patient’s gait changes, instability, aphasia, forgetfulness, hyperdystonia, and weight loss were all exacerbated since the initial hospital admission. The muscle tone of limbs increased significantly and became hyperactive. Pathological reflex examination revealed positive Babinski and Chaddock signs. There were no other positive neurological signs.

**Laboratory examinations**

A month prior to admission to our hospital, the patient was examined at the local hospital according to the test results provided by the patient. The results of cerebrospinal fluid (CSF) examination showed an elevated albumin level of 760 mg/L (nominal range 120-600 mg/L). No definitive diagnosis was made. When his progressive amnesia worsened, the patient was transferred to our hospital for further treatment. We conducted basic laboratory tests, including C-reactive protein, procalcitonin, erythrocyte sedimentation rate, full blood cell count, and electrocardiogram. Microbiological assays were negative, including screening tests for hepatitis, human immunodeficiency virus, and neurosyphilis. Immunological tests were also normal (Table 1).

To further clarify the diagnosis, we performed a second CSF examination. Cytology and biochemical parameters were within normal limits, but glucose and protein levels were slightly elevated (Table 2). The CSF virus test and bacterial culture were negative, allowing us to rule out central infectious diseases.

‘To rule out the possibility of a central tumor, an examination of paraneoplastic syndrome was actively carried out. The patient was examined before being readmitted to the hospital. Paraneoplastic syndrome (PNS) is an autoimmune syndrome caused by anti-neuron antibodies. Paraneoplastic syndrome should be considered if the patient shows dementia, extrapyramidal or cerebellar symptoms or other neurological symptoms, subacute onset or rapid progression, positive cerebrospinal fluid inflammatory markers, tumor risk factors or tumor family history [7]. The common antibodies are anti-Hu, anti-CV2, anti-Ri, anti-Ma2, anti-Yo, anti-NMDAR and anti-AMPAR antibodies. Different antibodies can indicate corresponding potential tumors. The most common disease associated with paraneoplastic syndrome is marginal lobular encephalitis, also known as paraneoplastic limbic encephalitis. Usually, the related antibodies are anti-Hu, anti-CV2, anti-Ma2, anti-Ri, and anti-Yo antibodies [8]. The patient was examined for paraneoplastic syndrome to find positive antibodies (Table 3).

**Imaging examinations**

Electroencephalography (EEG) showed generalized periodic sharp wave complexes and slow background activity. These findings were interpreted as nonspecific, moderate, widespread cortical dysfunction, also involving subcortical structures (Figure 1). Brain MRI showed no hemorrhage, infarction, or mass lesions. Diffusion-weighted imaging (DWI) detected increased signal intensity in the cortex of the right frontal-parietal lobe, part of the left frontal-parietal lobe next to the cerebral falx, cingulate gyrus, and bilateral temporal lobes. In addition, there was a high signal in the head of the left caudate nucleus (Figure 2).

**FINAL DIAGNOSIS**

The patient was diagnosed with CJD.

**TREATMENT**

According to the results, the patient’s inflammation index increased, and we carried out active anti-infective therapy, reduced intracranial pressure sedation, increased nutrition, and improved cognitive treatments. To avoid aspiration, treatment of the indwelling gastric tube was carried out. However, the condition did not improve. Brain biopsy was recommended to the family for confirmation of sCJD, but they declined and instead chose supportive care. Although we did not detect 14-3-3 protein, on the basis of clinical features and CSF, MRI, and EEG test results, the patient received a probable diagnosis of sCJD.
### Table 1 Laboratory test results

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Result</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Hu antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-CV2 antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Ri antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Ma2 antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Yo antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-ANNA-3 antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Tr antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-PCA-2 antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

### Table 2 The cerebro spinal fluid test results

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Result</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour</td>
<td>Colorless</td>
<td>Colorless</td>
</tr>
<tr>
<td>Transparency</td>
<td>Transparent</td>
<td>Transparent</td>
</tr>
<tr>
<td>Pan’s experiment</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>WBC count, × 10⁶/L</td>
<td>2</td>
<td>&lt; 8</td>
</tr>
<tr>
<td>RBC count, × 10⁶/μL</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrospinal fluid glucose, mmol/L</td>
<td>5.43</td>
<td>2.2-3.9</td>
</tr>
<tr>
<td>Cerebrospinal fluid protein, mmol/L</td>
<td>715</td>
<td>120-600</td>
</tr>
<tr>
<td>Cerebrospinal fluid chloride, mmol/L</td>
<td>125.4</td>
<td>120-152</td>
</tr>
<tr>
<td>Rubella virus IgG, IU/mL</td>
<td>0.68</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Anti-rubella virus IgM, COI</td>
<td>0.32</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Cytomegalovirus IgG, IU/mL</td>
<td>6.71</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Cytomegalovirus IgM, COI</td>
<td>0.16</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Epstein-Barr virus antibody</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Coxsackie virus antibody</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Nacterial smear (gram stain)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Acid-fast bacilli</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

WBC: White blood cell; RBC: Red blood cells.

**OUTCOME AND FOLLOW-UP**

The patient’s clinical status deteriorated over the subsequent week. However, the patient’s family opted for withdrawal of care, and he was discharged home.

**DISCUSSION**

CJD is a rare and fatal neurodegenerative disorder and represents the most common prion human disease. The pathogenesis of CJD is the conformational transition of a host-encoded cellular PrP into an infectious and pathogenic isoform that propagates in multiple regions of the brain by self-replication[1]. sCJD is the most common human prion disease, accounting for approximately 85% of all cases[2]. It is characterized by neuronal loss, astrogliosis, extensive spongiform degeneration, and deposition of misfolded PrP. The clinical characteristics include rapid progressive dementia,
Table 3 The cerebro spinal fluid paraneoplastic syndrome antibody test results

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Result</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Hu antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-CV2 antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Ri antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Ma2 antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Yo antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-ANNA-3 antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Tr antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-PCA-2 antibody IgG</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Figure 1 Electroencephalography shows diffuse slowing of background activity accompanied by intermittent slow triphasic waves with suggestion of periodic sharp wave complexes.

pyramidal tract signs, myoclonus, and psychiatric symptoms. There is a lack of specific symptoms at disease onset, especially psychiatric manifestations and rapid progressive dementia, and patients with CJD can be easily misdiagnosed[10].

Other neurological diseases, such as Alzheimer’s disease, dementia with Lewy bodies, and frontotemporal dementia, chronic course. Sometimes there is an acceleration in the course of the disease, but imaging changes can usually be distinguished. There were no characteristic changes in the head MRI scan, and through early EEG examination, a small number of patients can show a reduction in background wave amplitude, while most patients show a decrease in $\alpha$ waves and transient slow waves in the temporal lobe.

PNS is an autoimmune syndrome caused by anti-neuron antibodies. Diagnosis of PNS can be confirmed by the detection of anti-Hu, anti-CV2, anti-Ri, anti-Ma2, anti-Yo, anti-NMDAR and anti-AMPAR antibodies in the CSF, but in this case, these antibodies were all negative, so we ruled out PNS.

Due to the variable clinical presentation of CJD, which progresses rapidly without obvious clinical specificity, there is a need for prompt diagnosis and supportive treatment to avoid progression and extend the survival time. Our patient initially presented with mild amnesia symptoms, but when he was transferred to our hospital for treatment, the symptoms had progressed. At the same time, there were clinical manifestations indicating pyramidal tract involvement; cerebellar ataxia was the dominant feature at onset, followed by involuntary limb convulsions, which were rapidly followed by focal dystonia.

Clear diagnosis and elimination of other central nervous system diseases are very important for the diagnosis of CJD. Only inflammation indicators were elevated in the present case (Table 1). However, the patient was negative for Epstein-Barr virus antibodies, human immunodeficiency virus and neurosyphilis (Table 2). The second CSF examination ruled out infective encephalopathy, metabolic derangement, and autoimmune encephalopathy; all metabolic parameters were within normal limits. We were also able to rule out Alzheimer’s disease, frontotemporal dementia, and dementia with Lewy bodies based on the patient’s medical history (Table 3).
Figure 2 Magnetic resonance imaging of the patient’s brain. A-D: Diffusion-weighted imaging detected increase signal intensity in the cortex of right frontal-parietal lobe, part of the left frontal-parietal lobe next to the cerebral falx (A), cingulate gyrus (B), and bilateral temporal lobe (C and D). In addition, there was also a high signal in the head of left caudate nucleus (D).

EEG is an important and integral part of the CJD diagnostic process[11]. EEG recordings revealed gradual slowing of background activity with a more obvious appearance of bihemispheric triphasic waves and nearly typical periodic sharp wave complexes (Figure 1). The EEG diagnostic specificity and sensitivity for CJD are 64% and 91%, respectively[12]. Caobelli et al[12] reported that DWI may be the most sensitive imaging technique for early diagnosis, and MRI in general is the most helpful test for suspected sCJD, as it has excellent specificity and sensitivity[13]. Repeat brain MRI revealed increased signal intensity in the cortex and head of the left caudate nucleus. The typical DWI signal for early diagnosis of CJD is bilateral petal-like changes along the cortical sulcus (Figure 2). MRI has an overall sensitivity of 60%-70% and specificity of 80%-90%[14, 15]. It may be particularly reliable and helpful in the clinical diagnosis of patients with certain PrP genotypes.

Periodic sharp wave complexes are reported in EEG recordings of approximately two-thirds of patients with sCJD and are included in the World Health Organization (WHO) (1998) diagnostic classification criteria of sCJD. The diagnostic criteria for probable sCJD are: (1) rapidly evolving dementia (< 2 years); (2) typical periodic sharp wave complexes with triphasic morphology in EEG recordings and/or the presence of 14-3-3 protein in CSF examination; and (3) at least two of the following four clinical signs: (a) myoclonus; (b) ataxia and/or visual signs and symptoms; (c) extrapyramidal and/or pyramidal signs and symptoms; and (d) akinetic mutism. Patients with clinical signs of sCJD but without EEG and CSF abnormalities (either not present or investigation not available) are classified as having possible sCJD.

Some caution in performing autopsy should be mentioned due to the infective nature of prions. Eliminate known infected wounds and properly isolate the patient. There should be no use of contaminated food, and the contaminated equipment must be strictly disinfected. Used medical waste is burned separately.

Performing CSF examination, EEG, MRI, and 14-3-3 protein tests are important in the diagnosis of CJD. With regard to this case, neurological features included cerebellar ataxia, dementia, and myoclonus that rapidly progressed, with a short duration of illness. The patient’s condition deteriorated rapidly over a month, with clinical manifestations of pyramidal tract and memory dysfunction. Based on the patient’s clinical symptoms and EEG and MRI results and the WHO (1998) diagnostic classification criteria of sCJD, we diagnosed CJD.
CONCLUSION

CJD remains a particularly challenging diagnosis for physicians, mainly because of its rarity and clinical heterogeneity. sCJD is an uncommon and lethal disease that progresses quickly, and there is no effective treatment. Although brain biopsy is the gold standard for diagnosis, it is highly invasive, and not every family can accept it. For this reason, noninvasive examination is very important in diagnosis. These tests can be helpful in providing support for early diagnosis, but they do not change the prognostic. This case report aims to create awareness among physicians to emphasize the importance of pursuing an early diagnosis and identifying and reducing complications.

REFERENCES

Diagnosis, fetal risk and treatment of pemphigoid gestationis in pregnancy: A case report

Hai-Ning Jiao, Ye-Ping Ruan, Yan Liu, Meng Pan, Hui-Ping Zhong

ORCID number: Hai-Ning Jiao 0000-0001-8188-7798; Ye-Ping Ruan 0000-0002-3825-9662; Yan Liu 0000-0003-2171-8364; Meng Pan 0000-0003-4947-9369; Hui-Ping Zhong 0000-0002-0007-6799.

Author contributions: Jiao HN, Ruan YP and Zhong HP contributed to the planning, conduction and report of the work; Jiao HN, Ruan YP, Pan M and Zhong HP contributed to the conception and design of the work; Jiao HN, Liu Y and Zhong HP contributed to the acquisition of analysis and interpretation of the results; all authors have read and approved the 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 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).

Country/Territory of origin: China

Specialty type: Obstetrics and Gynecology

Abstract

BACKGROUND
Pemphigoid gestationis (PG) is a rare autoimmune blistering disease that usually presents in the second or third trimester, with an incidence of 1 per 50000 pregnancies. PG tends to recur with an earlier onset and a more severe course in subsequent pregnancies. Skin biopsy markers can be confirmed by direct immunofluorescence staining.

CASE SUMMARY
Our patient was diagnosed with PG at 8 mo of gestation with fresh bullous lesion marks on the abdomen and limbs. Termination of the pregnancy was performed by cesarean section at 37 + 4 wk of gestation. The patient delivered an infant weighing 3620 gm. The infant had urticaria-like and vesicular skin lesions and was diagnosed with PG. The patient was discharged on prednisolone and in a satisfactory condition. The infant was discharged after anti-inflammatory therapy for one week.

CONCLUSION
PG is a rarely reported disease, and 10% of newborns develop mild clinical symptoms consisting of urticaria-like or vesicular skin lesions. We intend to remind clinicians to consider this condition when a patient presents with such lesions so that treatment can be started early and neonatal morbidity can be taken into account.

Key Words: Pemphigoid gestationis; Pregnancy; Newborn; Pemphigus; Fluorescent antibody technique; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
Core Tip: Pemphigoid gestationis (PG) is a rarely reported disease, and 10% of newborns develop mild clinical symptoms consisting of urticaria-like or vesicular skin lesions. Our patient was diagnosed with PG at 8 mo of gestation and was performed by cesarean section at 37 + 4 wk of gestation. The infant had urticaria-like and vesicular skin lesions and was diagnosed with PG. We intend to remind clinicians to consider this condition when a patient presents with such lesions so that treatment can be started early and neonatal morbidity can be taken into account.

INTRODUCTION

Pemphigoid gestation (PG) is an autoimmune bullous disease that occurs during pregnancy or the puerperium [1]. The main clinical manifestations are tension blisters and bullae with urticaria-like plaques, accompanied by pruritus [2]. For approximately 14%-25% of patients in the postpartum period, menstrual periods and oral contraceptive drugs may induce or aggravate the disease [3]. PG can induce fetal growth restriction, premature delivery, and neonatal skin involvement. It has also been reported to cause low birth weight [4]. This disease is very rare, the clinical manifestation and laboratory examination results are similar to bullous pemphigoid, and the exact pathogenesis of PG has not been clarified.

CASE PRESENTATION

Chief complaints
A 30-year-old female presented with pruritic edematous erythema for 2 wk.

History of present illness
A 30-year-old female presented with a 2-wk history of pruritic edematous erythema on the trunk and extremities during her 32nd week of pregnancy with no inducing factors. These symptoms have never occurred before. She also had no history of drug or food allergies. Soon after, small bullae and vesicles developed at the periphery of the erythema; these healed readily with residual pigmentation (Figure 1).

History of past illness
The patient had no history of any previous disease.

Personal and family history
There was no family history of PG.

Physical examination
No mucosal lesions were observed. The Nikolsky sign was negative.

Laboratory examinations
Laboratory findings were normal, including hematocrit, urine analysis, hepatic and renal function, electrolytes, glycemia, anti-streptolysin and C-reactive protein.

Imaging examinations
Obstetric ultrasonography indicated no abnormality in the fetus.
A clinical diagnosis of PG was made. This was supported by histology that showed a dermoepidermal blister with conspicuous eosinophils within the blister and in the papillary dermis. Further investigation identified that the skin biopsy showed subepidermal blister with eosinophils and lymphocytes within the cavity and in the superficial dermis (Figure 2). Direct immunofluorescence (DIF) showed linear deposits of C3 along the basement membrane zone in the absence of IgG (Figure 3). Indirect immunofluorescence (IIF) was negative. Anti-BP180 was positive (90 normal range < 20 IU/mL), and anti-BP230 was negative. Thus, a diagnosis of PG was made.

Prednisone was administered orally at a dose of 25 mg. Four weeks later, the prednisone was tapered to 20 mg gradually with no new lesions appearing. Many red spots and pigmentation were left on the body and limbs. During the pregnancy, regular prenatal visits were conducted to help to monitor the health of the patient and her baby.

A multidisciplinary (obstetrics, dermatology, pathology, and neonatology) discussion was initiated during the patient’s late pregnancy (37 wk of pregnancy) to determine the timing and method of delivery. For this patient with obstetrical factors (scarred uterus), a cesarean section at 37 + 4 wk of gestation was recommended. All the decisions were fully communicated with the patient and her family members. The Apgar score of the infant was 10 points, and the weight of the infant was 3620 g. After the placenta was delivered, a pathology specimen and umbilical cord blood was collected for examination. Prednisone was administered orally at a dose of 20 mg with no postoperative symptoms.

After examining the newborn, we found that the infant had vesicles and pustules on the palms and soles and erosions on the face and trunk (Figure 4). The skin biopsy showed another layer of epithelium over the normal epithelium with eosinophil and lymphocyte infiltration (Figure 5). DIF showed linear deposits of C3 along the basement membrane zone, similar to that observed in the mother (Figure 6). Anti-BP180 was positive (100 normal range < 20 IU/mL). Anti-BP230 was negative.

Intensive monitoring and anti-infection treatment with penicillium legume intravenous injection for the infant were given. With local use of astringent and bactericidal drugs, the infant’s rash gradually improved after 1 wk (Figure 7).

PG can be diagnosed in several ways: clinical symptoms, histological findings, DIF or IIF, and enzyme-linked immunosorbent assay. In our patient, DIF showed a linear
Jiao HN et al. Pemphigoid gestationis in pregnancy

Figure 2 Skin with a sub-epidermal blister with eosinophils and lymphocytes within the cavity and in superficial dermis of pemphigoid gestationis in pregnancy (hematoxylin and eosin 100×).

Figure 3 Linear deposition of C3 along the basement membrane zone with the absence of IgG (direct immunofluorescence) of pemphigoid gestationis in pregnancy.

deposit of C3 along the basement membrane zone in the absence of IgG. In a retrospective study of 25 cases of PG, fourteen patients presented the same DIF pattern as our patient[5]. Linear C3 deposits were observed in 100% of patients, and linear IgG deposits were observed in 25%-50% of patients, which indicated that C3 was pathognomonic to the disease[3]. This is the most important and commonly used PG detection method[6].

Treatment, which prevents the formation of herpes and controls itching symptoms depends on the stage and severity of the disease[7]. Topical glucocorticoids and orally administered antihistamine drugs can be used in mild cases. Oral corticosteroids (prednisone 0.5-1 mg/kg/d) or even intravenous gamma globulin may be used in severe cases[8]. PG is usually in remission for weeks to months after delivery, with a few cases extending to 2 years after delivery.

Most pregnant women with PG can deliver a healthy newborn after full-term pregnancy, via natural delivery or cesarean section for obstetric indications[8]. Due to the passive transfer of IgG1 antibody from mother to fetus, 10% of newborns with PG develop clinical symptoms, including urticaria or vesicular skin lesions, and have an increased risk of premature delivery and low birth weight[10]. There is no evidence of an association between medication regimens and fetal outcomes, and adverse pregnancy outcomes appear to be more closely associated with higher antibody titers in maternal serum and neonatal cord blood[11].

In this patient, multidisciplinary (obstetrics, dermatology, pathology, and neonatology) discussion was initiated during the patient’s late pregnancy (37 wk of pregnancy) to determine the timing and method of delivery. For this patient, who had obstetrical factors, a cesarean section at 37 + 4 wk of gestation pregnancy was recommended.

The newborn had vesicles and pustules on the palms and soles and erosions on the face and trunk. Her oral mucosa was not involved, and the skin lesions subsided rapidly without any proliferative changes. Therefore, the clinical manifestations of skin lesions in the infant were significantly different from those in the mothers.
Additionally, anti-BP180 was positive (100 normal range < 20 IU/mL) and significantly higher than that of the mother. The diagnosis was confirmed by referencing the clinical history, histopathological examination and immunofluorescence examination of the mother and the infant. Neonatal pemphigoid is a self-healing disease, and most infants can resolve the skin lesions within 1 mo, so the treatment is mainly symptomatic treatment to prevent secondary infection of skin lesions. Short-term topical use of glucocorticoids may be considered for those with more frequent rashes. In this case, no special treatment was given to the infant, and the skin lesion subsided rapidly.

CONCLUSION
PG is a rarely reported disease, and 10% of newborns develop mild clinical symptoms consisting of urticaria-like or vesicular skin lesions[12]. We intend to remind clinicians to consider this condition when a patient presents with such lesions so that treatment...
Figure 6 Direct immunofluorescence of the infant showed linear deposits of C3 along the basement membrane zone similar to her mother.

Figure 7 The seventh day after birth of the infant.

can be started early and neonatal morbidity can be taken into account.

In the management of pregnant women with PG, a multidisciplinary team should be assembled quickly to develop a treatment plan; obstetricians, dermatologists, pediatricians, and pathologists should collaborate in the multidisciplinary approach to treating maternal, fetal, and neonatal complications.

ACKNOWLEDGEMENTS

The authors thank the Rui-Jin Hospital, Shanghai Jiao Tong University School of Medicine for their assistance with this research.

REFERENCES


Histology transformation-mediated pathological atypism in small-cell lung cancer within the presence of chemotherapy: A case report

Qing Ju, Ying-Tong Wu, Yong Zhang, Wen-Hui Yang, Cheng-Lei Zhao, Jian Zhang

Abstract

BACKGROUND
The treatment of small-cell lung cancer (SCLC) has progressed little in recent years because of its unique biological activities and complex genomic alterations. Chemotherapy combined with radiotherapy has been widely accepted as the first-line treatment for SCLC.

CASE SUMMARY
Here, we present a 68-year-old male smoker who was diagnosed with SCLC of the right lung. After several cycles of concurrent chemoradiotherapy, the tumor progressed with broad metastasis to liver and bone. Histopathological examination showed an obvious transformation to adenocarcinoma, probably a partial recurrence mediated by the chemotherapy-based regimen. A mixed tumor as the primary lesion and transformation from SCLC or/and tumor stem cells may have accounted for the pathology conversion. We adjusted the treatment schedule in accord with the change in phenotype.

CONCLUSION
Although diffuse skeletal and hepatic metastases were seen on a recent computed tomography scan, the patient is alive, with intervals of progression and shrinkage of his cancer.

Key Words: Small-cell lung cancer; Adenocarcinoma; Transformation; Chemotherapy; Case report
INTRODUCTION
Small-cell lung cancer (SCLC) is a subtype of lung cancer because of its histology and morphology, and it accounts for 15%-20% of newly diagnosed cases worldwide every year[1]. Owing to its rapid growth and progression, it is often diagnosed at an advanced stage by histopathological examination, indicating a life expectancy of less than 1 year. As for treatment, there is a consensus that normative chemotherapy and appropriate-dose radiotherapy lead to high response rate in a clinical pathology selection-dependent manner that is recommended by American Society of Clinical Oncology[2,3]. It should be noted that targeted therapy and immunotherapy, which are likely to be effective in the treatment of non-SCLC (NSCLC)[4], are not recommended for SCLC because of the absence of mutation-driven evolution and its characteristic histological and molecular features[5]. However, histological transformation is likely to change the treatment strategy, facilitating appropriate and rational decisions in SCLC management. Here we present a male patient with an initial diagnosis of SCLC who developed metastatic adenocarcinoma, a subtype of NSCLC, after standard chemotherapy regimens. He has survived for 76 mo since the first diagnosis, which longer than expected.

CASE PRESENTATION
Chief complaints
A 68-year-old man with a smoking history of 40 pack-years came to seek medical advice in light of cough, expectoration, and shortness of breath.

History of present illness
A contrast-enhanced computed tomography (CT) scan of the chest (which cannot be found at present) indicated a malignant tumor of the lung. Ultrasound-guided percutaneous biopsy confirmed the lesion characteristics and histopathology. At high magnification, cells in two biopsy samples of same lesion were uniform in size and arrangement, fusiform in shape with hyperchromatic nuclei (Figure 1D), and having an aggressive growth pattern. Coupled with immunohistochemistry (IHC), these results indicated a SCLC diagnosis (Figure 2). Molecular pathology was tested by amplification-refractory mutation system (ARMS)-PCR, which indicated an absence of sensitive mutation (Supplementary Figure 1A). According to the American Society of Clinical Oncology Endorsement of the American College of Chest physicians guidelines, the patient was treated with concurrent chemoradiotherapy consisting of six cycles of etoposide and carboplatin with thoracic radiotherapy D45Gy/30F twice per day. After treat, his clinical symptoms improved and the lesion in the right lower lobe shrank dramatically on CT scanning (Figure 1A).

History of past illness
The patient suffered from chronic obstructive pulmonary disease, hypertension, and diabetes for at least 10 years. As they were not thought to be associated with the progression of lung cancer, we did not include a detailed description in this article.

Core Tip: In this report, we present a male patient with a diagnosis of small-cell lung cancer (SCLC) who developed metastatic adenocarcinoma, a subtype of non-SCLC, after standard chemotherapy regimens. He has survived for 90 mo since the first diagnosis, which is longer than expected.

Citation: Ju Q, Wu YT, Zhang Y, Yang WH, Zhao CL, Zhang J. Histology transformation-mediated pathological atypism in small-cell lung cancer within the presence of chemotherapy: A case report. World J Clin Cases 2021; 9(34): 10652-10658
URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10652.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10652
Laboratory examinations
The presence of bilateral pulmonary interstitial hyperplasia and inhomogeneous emphysema were consistent with tumor progression and deterioration of the patient’s condition. Ultrasound-guided percutaneous biopsies were performed to determine the reason why the standard SCLC treatment did not have a curative effect. The tumor cells were ovoid with hyperchromatic nuclei and arranged in strips or nests (Figure 1E). Immunohistochemistry (IHC) indicated poorly differentiated adenocarcinoma owing to the presence of some specific pathological markers (Figure 2). What needed more attention was that several SCLC markers, such as thyroid transcription factor (TTF)-1, cytokeratin (CK)5/6, and P40, were expressed only in individual cells, and Ki-67-positive cells accounted for more than 25%, indicating rapid growth and proliferation of tumor cells. Genetic analysis found that the patient had no epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement (D5F3 Ventana IHC). However, repeated molecular pathology showed that after standard chemotherapy, the patient bore a KRAS mutation (Supplementary Figure 1B), which corresponded with the histology findings. Four cycles of cisplatin and pemetrexed achieved a decrease in the size of the lesion in the right lower lung, which further supported the diagnosis of adenocarcinoma.

Imaging examinations
With the remission of clinical symptoms, the patient failed to continue regular follow-up and periodic imaging. It was beyond our expectation that the patient suffered thoracalgia in the lower right chest 3 years after the last CT examination. A CT examination of his chest indicated growth and consolidation of the lesion in the lower right lung, with scattered nodules, and right inferior lobe insufficiency compared with a CT obtained 3 years previously. (Figure 1B).

FINAL DIAGNOSIS
Advanced lung cancer.

TREATMENT
After the patient stopped treatment, he experienced persistent dull pain in the right hypochondriac region and back with no noticeable improvement after odynolysis. Follow-up imaging revealed that the parietal pleura were eroded by invasive
Figure 2 Immunohistochemical staining of three biopsies. Several typical biomarkers of small-cell lung cancer were examined repeatedly at different stages. Synaptophysin, chromogranin A, CD56 and TTF1 indicate histological transformation. Magnifications are × 40; The scale bar is 50 μm.

Figure 2 Immunohistochemical staining of three biopsies. Several typical biomarkers of small-cell lung cancer were examined repeatedly at different stages. Synaptophysin, chromogranin A, CD56 and TTF1 indicate histological transformation. Magnifications are × 40; The scale bar is 50 μm.

malignant cells, and that there was a strong possibility that tumor cells had invaded bone, brain, liver, and local and distant lymph nodes. According to the patient’s condition and his tolerance of chemotherapeutic drugs, nedaplatin plus pemetrexed, together with intermittent local radiation, were seen as the best treatment choice. After several cycles, the clinical manifestations were improved. However, after a 4 mo interval, CT revealed that the solid pulmonary nodules in the right lung had enlarged, pleural effusion had emerged in the right thoracic cavity, and a nodule embedded in upper lobe of the left lung had progressed, all of which indicated tumor progression (Figure 1C). A third ultrasound-guided biopsy of the same nodules in the right lung found large cells with hyperchromatic nuclei arranged as in an adenoma, and with aggressive characteristics (Figure 1F). IHC staining and molecular examination supported the previous diagnosis of adenocarcinoma of the lung (Figure 2 and
Combination treatment with nedaplatin and pemetrexed were continued for two cycles, until the patient reported the appearance of blood in the phlegm.

**OUTCOME AND FOLLOW-UP**

Subsequently, pemetrexed was substituted for docetaxel in previous therapeutic schedule in several cycles to now. At this time, the patient is alive 76 mo after the definitive diagnosis.

**DISCUSSION**

It is well known that SCLC accounts for a small proportion of newly diagnosed lung cancer worldwide every year. The incidence is the highest in male and female smokers, and SCLC has a high mortality less than 1 year after diagnosis[1]. On the basis of the location of the lesion and distant metastasis, SCLCs are generally staged as limited and extensive disease, which have different prognoses and treatment schedules. Its characteristic rapid progression and late diagnosis as metastatic disease determine its poor prognosis, with a median survival of 3 mo in untreated patients. A high response rate and sensitivity to chemotherapy and radiotherapy make it possible to alleviate SCLC to some extent, but lead to relapse within the first year after chemoradiotherapy[6].

Even though genome-based diagnosis has increased the options for targeted therapy for NSCLC patients, SCLC treatment options remain limited to regimens based on chemotherapy and radiotherapy. In addition, therapeutic effectiveness varies with the patient’s condition, drug dose and frequency, and the quantity of radiation. It is noteworthy that, compared with NSCLC, biomolecular aberrations such as mutations of EGFR, KRAS and BRAF genes or ALK gene rearrangements are rare in SCLC, which leads to a lack of indications for the use of tyrosine kinase inhibitors[7]. Instead, mutations of genes involved in p53 and RB and deletions or increased copy number in specific chromosomes contribute to carcinogenesis, and few effective, targeted drugs are available[8]. Surprisingly, a recent study reported that atezolizumab, a programmed cell death ligand 1 (PD-L1) inhibitor of immunotherapeutic drugs, combined with etoposide and carboplatin extended overall survival of SCLC patients and has been approved as first-line treatment of advanced-stage SCLC, indicating the feasibility of immunotherapy to extend the life expectancy of SCLC patients[9].

In this case, the biopsy had SCLC characteristics, and the patient received several cycles of combination treatment with chemotherapy plus radiotherapy. A second biopsy of the same lesion was found to be adenocarcinoma of lung cancer. Other than improper procedures and ineluctable errors in drawing samples, there are several explanations for this phenomenon. (1) The first involves mixed types of lung cancer at the initial diagnosis. After combined treatment with chemotherapy and radiotherapy, the dominant SCLC component was suppressed or eliminated, leading to development of the adenocarcinoma component. Although both are sensitive to platinum-based drugs, SCLC is more vulnerable to chemotherapy compared with other types of lung cancer. However, the first histological examination revealed no significant expression of adenocarcinoma-related biomarkers in either of two samples from the same lesion. Furthermore, comparison of the two biopsies found that there were indeed different types of lung cancer in the same lesion, which excludes mixed tumors in this case; (2) The second explanation is histopathological transformation from SCLC to NSCLC. It has been widely reported that transformation from EGFR-mutated NSCLC to SCLC while using tyrosine kinase inhibitors (TKIs) is a potential mechanism to mediate resistance to targeted drugs[8]. Histological transformation in SCLC is rarely reported, however. Three biopsies were obtained from this patient, and IHC staining and molecular pathology revealed changes in particular biomarkers that indicated histological transformation of the lung cancer. Moreover, switching the treatment regimen based on the histopathological results alleviated the clinical manifestations, which further supported our previous diagnosis; and (3) The third is tumor stem-cell oriented adenocarcinoma. Tumor stem cells are liable to be stimulated in particular circumstances, leading to differentiation, proliferation, and the formation of lesions[10,11]. However, given that the number of stem cells is limited and the methods of detection are not well advanced, tumor stem-cell oriented adenocarcinoma...
should also be taken into account. In this patient, repeated biopsies indicated a possibility that he experienced an SCLC-NSCLC transformation, mainly because of pathology-oriented diagnosis and variable characteristics on CT scans. Although a rational diagnosis of histological transformation is not possible without surgical samples, it is seemingly proper to take transformation into account after excluding other underlying possibilities. Further verification is needed.

CONCLUSION

Our experience with this case highlights several key points that are critical for clinical diagnosis and treatment. The first is the necessity for several ultrasound- or CT-guided biopsies. Repeated biopsies dynamically monitor phenotypic alterations of tumor cells, which facilitates the use of appropriate treatment regimens. Secondly, sampling multiple sites in primary and metastatic organs contributes to increased accuracy of diagnosis, avoiding the limitation of single site. In this patient, samples at different lesions in first biopsy helped to determine the presence of a mixed tumor or only one type of tumor cell. Thirdly, genetic analysis or DNA sequencing help physicians to diagnose pathology, select the best treatment schedule, and assess patient prognosis. Somatic mutations in several oncogenes, including EGFR, ALK, ROS1, and others, drive abnormal proliferation of mutant cells that can be targeted by TKIs, even though the mutations are rare in SCLC. Detecting mutations is conducive to discovering histological transformation and expanding therapeutic alternatives. Finally, the implementation of standard diagnostic and therapeutic programs is important to inhibit the development of malignant lesions and further improve healing.

REFERENCES


11 Banks-Schlegel SP, Gazdar AF, Harris CC. Intermediate filament and cross-linked envelope expression in human lung tumor cell lines. *Cancer Res* 1985; 45: 1187-1197 [PMID: 2578876]
Reversible congestive heart failure associated with hypocalcemia: A case report

Chu Wang, Li-Wen Dou, Tian-Bing Wang, Yang Guo

BACKGROUND
Hypoparathyroidism is a rare disease that may occur due to primary or secondary etiologies. The estimated incidence in the United States is 24–37/100000 person-years. Congestive heart failure associated with hypocalcemia due to hypoparathyroidism is an even rarer presentation.

CASE SUMMARY
Here, we present a 64-year-old woman with congestive heart failure following hypocalcemia. The patient was transferred to our emergency department with complaints of rapidly progressive dyspnea, shortness of breath and heaviness of the chest for 4 d. She had a history of undergoing thyroidectomy and partial tracheotomy 2 years prior due to a malignant thyroid tumor. Muscle spasms had been present 1 year ago, and cataracts were treated with intraocular lens replacement in both eyes. Most tests were within normal ranges, except serum calcium at 1.33 mmol/L (2.20–2.65 mmol/L), ionized calcium at 0.69 mmol/L (1.15–1.29 mmol/L), and parathyroid hormone at < 1.0 pg/mL (12–88 pg/mL). Echocardiography revealed an ejection fraction of 28.48%. Cardiac function was quickly reversed by restoring the serum calcium concentration. Significant improvements were noted with an ejection fraction of up to 48.50% at follow-up.

CONCLUSION
For patients with potential hypocalcemia, monitoring calcium levels and dealing with hypocalcemia in time to avoid serious complications are important.

Key Words: Hypoparathyroidism; Congestive heart failure; Cardiomyopathy; Parathyroid hormone; Calcium; Echocardiography; Case report
©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Hypoparathyroidism-related cardiomyopathy is rare but reversible. We present a rare case of congestive heart failure associated with hypocalcemia in an elderly female with a history of thyroidectomy. The heart failure was reversed rapidly by infusion of calcium gluconate. With the supplementation of calcium, the cardiac function was maintained very well. The patient also presented with a history of cataracts. This case highlights that, for patients with potential hypocalcemia, we need to supplement calcium and closely monitor calcium levels to manage the hypocalcemia in time to avoid serious complications, such as cardiac complications or cataracts.

INTRODUCTION

Hypoparathyroidism is a rare disease that may occur due to primary or secondary etiologies. The level of parathyroid hormone is low; therefore, serum concentrations of calcium and phosphorus cannot be maintained within a narrow normal range, resulting in hypocalcemia and hyperphosphatemia[1]. Hypocalcemia has many manifestations, such as muscle spasms, hair loss, dry skin and brittle nails[2]. Here, we present a case of chronic hypocalcemia-induced cardiomyopathy following hypoparathyroidism, manifesting as congestive heart failure (CHF), which was quickly reversed by restoring the serum calcium concentration (Table 1).

CASE PRESENTATION

Chief complaints

A 64-year-old woman was transferred to the emergency department on October 30, 2020 with complaints of insidious onset but rapidly progressive dyspnea, shortness of breath and heaviness of the chest for 4 d.

History of present illness

The patient had progressive dyspnea and shortness of breath without obvious cause on October 26, 2020. Symptoms were present during activity or at rest, which could last for about 1 h and then resolve spontaneously. There was no fever, cough, sputum, chest pain, hemoptysis, or lower limb edema. On October 29, 2020, she went to a local hospital for symptom aggravation, and congestive cardiac failure was diagnosed. Diuretic treatment was adopted. No effect was observed. Thereafter, she was transferred to our hospital for further evaluation and treatment.

History of past illness

She had a history of undergoing thyroidectomy and partial tracheotomy in 2018 due to a malignant thyroid tumor, followed by iodine-131 radiotherapy every 6 mo thereafter (3 times in total). Intraocular lens implantation was performed in both eyes in 2019 due to cataracts. Muscle spasms were also present in 2019. Diabetes mellitus was noted. She was taking levothyroxine (175 μg qd), calcium carbonate (0.5 g tid) and acarbose (100 mg qd) regularly.

Personal and family history

Personal and family history were unremarkable.

Physical examination

On general physical examination, the patient was conscious with a blood pressure of 140/80 mmHg, respiratory rate of 16 breaths/min, and pulse rate of 104 beats/min.
Table 1 Timeline of the case

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Events</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>Thyroidectomy and partial tracheotomy</td>
<td>Iodine-131 radiotherapy every six months thereafter (3 times in total)</td>
</tr>
<tr>
<td>June 2019</td>
<td>Muscle spasms</td>
<td>Intraocular lens implantation in both eyes due to cataracts</td>
</tr>
<tr>
<td>October 26, 2020</td>
<td>Rapidly progressive dyspnea, shortness of breath</td>
<td>Treated for CHF at a local hospital without any effect</td>
</tr>
<tr>
<td>October 30, 2020</td>
<td>Transferred to our ER department</td>
<td>-</td>
</tr>
<tr>
<td>November 1, 2020</td>
<td>Symptoms resolved greatly</td>
<td>Administration of a 10% calcium gluconate</td>
</tr>
<tr>
<td>December 2, 2020</td>
<td>Follow up 1 mo later</td>
<td>Oral calcium carbonate (0.75 g qid) and calcitriol (0.25 μg bid)</td>
</tr>
</tbody>
</table>

CHF: Congestive heart failure.

Figure 1 Electrocardiography on admission showed a prolonged QT interval corrected for heart rate. The QT interval corrected for heart rate equaled 0.560 s.

Auscultation revealed reduced air entry in both lungs. Edema of the lower limbs was noted. No cyanosis, clubbing or lymphadenopathy were observed. Abdominal and central nervous system examinations were unremarkable.

Laboratory examinations
The following levels (normal range) were revealed. Routine blood test showed hemoglobin was 116 g/L (115–150 g/L). Biochemical tests revealed serum calcium was 1.33 mmol/L (2.20–2.65 mmol/L), ionized calcium was 0.69 mmol/L (1.15–1.29 mmol/L), phosphorus was 2.43 mmol/L (0.81–1.45 mmol/L), serum magnesium was 0.67 mmol/L (0.7–1.05 mmol/L), albumin was 38.8 g/L (40–55 g/L), total bilirubin was 9.3 μmol/L (3–21 μmol/L), and creatinine was 65 μmol/L (45–84 μmol/L). Infection related markers showed that C-reactive protein was 11.1 mg/L (0–10 mg/L), procalcitonin was 0.071 ng/mL (< 0.5 ng/mL). Cardiac-related markers showed that B-brain natriuretic peptide was 730 pg/mL (0–100 pg/mL). High-sensitivity troponin, myoglobin and creatine kinase MB were within normal ranges. Parathyroid hormone was < 1.0 pg/mL (12–88 pg/mL). The arterial blood gas level was within normal limits.

Imaging examinations
Electrocardiography on admission showed a prolonged corrected QT interval (0.560 s) (Figure 1). Chest computed tomography showed bilateral lung infection, mild enlargement of the left atrium and ventricle, and bilateral pleural and pericardial effusions (Figure 2). Head computed tomography showed bilateral symmetric calcification in the basal ganglia (Figure 3). Echocardiography revealed that the left heart was enlarged with reduced movement of the left ventricle and a small amount of pericardial effusion with an ejection fraction (EF) of 28.48% on admission (Figure 4).
Figure 2 Chest computed tomography on admission showed bilateral lung infection and bilateral pleural effusions. Black arrows showed bilateral pleural effusion; White arrows showed bilateral lung infection.

Figure 3 Head computed tomography on admission showed symmetric calcification in basal ganglia. No sign of infraction or hemorrhage was observed; White arrows: Calcification.

Figure 4 Echocardiography on admission. Left ventricular enlargement and left ventricular systolic function was significantly reduced. The ejection fraction was 28.48%.

**FINAL DIAGNOSIS**

The final diagnosis of the presented case was CHF associated with hypocalcemia and hypoparathyroidism. Myocardial infarction and pulmonary heart disease were excluded based on the history, electrocardiography, echocardiography and chest computed tomography.
Figure 5 Echocardiography 2 d after admission. Left ventricular systolic function improved after calcium supplementation. The ejection fraction was 40.80%.

**TREATMENT**

The patient was administered a 10% calcium gluconate 100 mL (930 mg of elemental calcium) infusion in 1000 mL of 5% dextrose at a rate of 50 mL/h. Within 2 d, the serum calcium level increased from 1.33 mmol/L to 2.14 mmol/L, ionized calcium level increased from 0.69 mmol/L to 1.11 mmol/L, and echocardiography showed an EF of 40.80% (Figure 5).

**OUTCOME AND FOLLOW-UP**

The symptoms of CHF were quickly alleviated. The patient was then discharged with oral calcium carbonate (0.75 g qid) and calcitriol (0.25 μg bid). At the 1-mo follow-up, the patient had no symptoms of CHF, and echocardiography showed an EF of 48.50% (Figure 6). At the 4-mo follow-up, the patient had no symptoms of CHF, and echocardiography showed left heart size and left ventricular systolic function returned to normal with no pericardial effusion. EF was 65.60% (Figure 7).

**DISCUSSION**

Hypoparathyroidism is a relatively uncommon disease. The estimated incidence in the United States is 24–37/100000 person-years[3]. It is characterized by hypocalcemia due to absent or low parathyroid hormone levels. The major function of parathyroid hormone is to maintain the level of serum calcium by binding to cell surface receptors in the bone and kidneys, thereby modulating the calcium concentration in the blood. Approximately 75% of cases are due to neck surgery[3]. Other etiologies include autoimmune diseases or hereditary hypoparathyroidism, such as DiGeorge syndrome, autosomally inherited hypoparathyroidism and autoimmune polyglandular syndrome type I.

Our patient had undergone extensive thyroid surgery 2 years prior and had developed symptoms of hypoparathyroidism for 1 year, even though she was taking calcium carbonate. With prolonged duration of hypocalcemia, dilated cardiomyopathy, a severe complication, developed, which was rapidly and easily reversed by calcium supplementation. Severe complications of hypocalcemia include confusion, muscle spasms, numbness in the hands, feet and face, depression, hallucinations, muscle cramps, brittle nails, and an increased risk of bone fractures. Dilated cardiomyopathy caused by hypocalcemia is very rare but reversible[4,5]. Unfortunately, the reversibility might not be complete[4]. Fortunately, cardiac function was fully restored after supplementation of calcium. Normal levels of calcium are critical for cardiac function and for the reduction in mortality[6].

The patient underwent surgery in both eyes for cataracts, which might also have been a manifestation of her prolonged hypocalcemia. The proposed mechanism of cataract formation from hypocalcemia is membrane damage due to low calcium levels in the aqueous humor and increased sodium levels in the lens[7]. Sharp vigilance about the possibility of cataracts induced by hypocalcemia should be maintained, although diabetes mellitus may also contribute to cataract formation[8].
In conclusion, prolonged hypocalcemia should be avoided, especially in patients after thyroid surgery. For patients with hypoparathyroidism, serum calcium be monitored along with regular ophthalmic checks. CHF may develop following hypoparathyroidism and cataracts.

CONCLUSION
For patients with potential hypocalcemia, we need to supplement calcium and closely monitor serum calcium levels to manage hypocalcemia in time to avoid serious complications, such as cardiac complications or cataracts.

REFERENCES

Excimer laser coronary atherectomy for a severe calcified coronary ostium lesion: A case report

Fang-Jie Hou, Xiao-Teng Ma, Yu-Jie Zhou, Jun Guan

ORCID number: Fang-Jie Hou 0000-0002-4859-9804; Xiao-Teng Ma 0000-0003-4806-6458; Yu-Jie Zhou 0000-0002-9545-1984; Jun Guan 0000-0001-9642-1595.

Author contributions: Hou FJ followed up the patient and was a major contributor to manuscript writing; Guan J, Zhou YJ and Ma XT analyzed the patient data and angiography data; all authors 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 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).

Country/Territory of origin: China

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Diagnosis: Excimer laser coronary atherectomy; Coronary ostium lesion; Coronary calcified lesion; Intravascular ultrasound; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
Core Tip: In the presented case, coronary angiography showed severe calcific stenosis (approximately 90%) in the right coronary artery ostium. A 2.5 mm × 12.0 mm balloon was unable to be advanced into the lesion, while a 2.0 mm × 12.0 mm balloon could not be inflated in the right ostium. Intravascular ultrasonography revealed severe calcifications. The patient underwent an excimer laser coronary atherectomy (ELCA) and balloon dilation, and remained asymptomatic during the 12-mo follow-up. This is the first case report of the successful use of ELCA and small balloon dilatation in treating a severely calcified cardiac ostium lesion.

INTRODUCTION

Excimer laser coronary atherectomy (ELCA) has emerged as a key procedure that can modify coronary plaques. ELCA achieves its therapeutic efficacy primarily through its photochemical, photothermal, and photomechanical actions. It was reported by Phillips that there were approximately 50000 ELCA catheters used during the period of 2010–2019[1]. However, reports on the use of ELCA in treating heavily calcified coronary lesions are scarce.

CASE PRESENTATION

Chief complaints

An 81-year-old male presented to the Cardiology Department of Qingdao Municipal Hospital with a 1-year history of chest pain.

History of present illness

Coronary angiography (CAG) carried out in a separate center three months earlier noted severe calcific stenosis (approximately 90%) in the right coronary artery (RCA) ostium, 90% stenosis in the proximal left circumflex artery, and 90% stenosis in the proximal left anterior descending artery. The patient declined coronary artery bypass grafting. Stent insertion was then performed in each of the occluded arteries. However, the RCA ostium was unable to be advanced using a 2.5 mm × 12.0 mm balloon (NC Sprinter, Medtronic, United States) or dilated using a 2.0 mm × 12.0 mm balloon (Sprinter, Medtronic, United States). The patient still had persistent angina pectoris despite the insertion of two stents.

History of past illness

The patient had hypertension for more than 30 years, diabetes mellitus for over 7 years, and had no history of smoking.

Personal and family history

The patient had no personal or family history.

Physical examination

No positive signs were found during the physical examination.

Laboratory examinations

No abnormalities were found during laboratory examinations.

Imaging examinations

Percutaneous coronary intervention was performed for the RCA ostium lesion after informed consent was obtained from the patient. The radial artery was cannulated using a 6-Fr SAL1.0 guiding catheter (Medtronic, United States). The distal RCA was
then cannulated with a Balance Middle Weight Universal II guidewire (Abbott, United States). Intravascular ultrasonography (IVUS; Boston Scientific, United States) was performed and identified severe calcifications (Figure 1A-D).

**FINAL DIAGNOSIS**

CAG and IVUS revealed severe calcific stenosis in the RCA ostium.

**TREATMENT**

A 0.9 mm eccentric catheter (Spectranetics, United States) was used to initiate ELCA at 45/60, 60/80, and 80/80 (fluence/Hz) in sequence. This initially resulted in no progress. A 1.5 mm × 15.0 mm balloon (Sprinter, Medtronic, United States) was adopted to dilate the lesion at 10–12 atm. At 45/60 (fluence/Hz), the catheter was slowly passed through the lesion (Figure 1E). The laser catheter was inserted at a speed of less than 0.5-1.0 mm/s using a “saline flush” technique. Normal saline was flushed into the guiding catheter and manifold before laser treatment, and a 5-10 mL bolus of saline was injected prior to each train of laser pulses through the guiding catheter. Continuous saline flushing at a rate of 1-2 mL/s was performed during laser treatment[2,3]. The lesion was then successfully dilated using a 2.5 mm × 12 mm balloon (NC Sprinter, Medtronic, United States). One 3.50 mm × 18.00 mm stent (Xience Xpedition; Abbott) was placed at 12 atm (Figure 1F). The stent was deployed at 14-20 atm to perform post-dilation with a 3.5 mm × 12.0 mm balloon. Stent placements were evaluated with CAG, and the final IVUS findings demonstrated no obvious dissection, malposition, or under expansion (Figure 1G-J).

**OUTCOME AND FOLLOW-UP**

The patient was healthy and asymptomatic after operation during hospitalization and remained asymptomatic during the 1, 3, 6, and 12-mo follow-up visits.

**DISCUSSION**

Coronary artery ostial lesions are barriers to the percutaneous coronary interventions, especially in the presence of severe calcifications. In most cases, severe coronary artery calcifications cannot be crossed or expanded with balloons despite the successful advancement of the guidewire distal to the lesion. ELCA and rotational atherectomy are the two treatments that are effective in managing severe coronary artery calcifications. The risk of no reflow is very low because most of the particles produced by ELCA are less than 10 μm in diameter, which can easily be filtered by the reticuloendothelial system[4]. The dissection of ostium lesions is likely to cause more serious consequences. The use of 308 nm pulsed ultraviolet light reduces the risk of vessel perforation and dissection, given its shallow penetration depth. Most standard 0.014-inch guidewires are compatible with ELCA. Lesions that are unable to be cannulated or expanded may benefit from the use of a 0.9 mm X-80 catheter with a maximum fluence (energy) of 80 mJ/mm² and repetition rate of 80 Hz, both of which are attainable using a 10 s on and 5 s off laser cycle[1]. Calcified lesions are amenable to treatment with a 0.9 mm excimer laser catheter bringing increased density of energy while conserving the production of heat, which results in a smaller ablated area. The laser catheter pushing speed should be less than 0.5-1.0 mm/s to avoid production of large particles.

Currently, ELCA is commonly used in highly complex lesions, including saphenous vein grafts, calcifications, tortuosity (moderate/severe), in-stent restenosis, and bifurcations, and carries the dual benefit of low rates of major adverse cardiovascular complications and high technical and procedural success rates[5,6]. We present the first case of a severe calcified ostium lesion treated with ELCA and balloon dilatation. During the ELCA procedure, if the catheter cannot pass through the lesion smoothly, balloon dilatation can be used to change the plaque morphology and achieve better results. Although ELCA may not be the first choice for severe calcified coronary
Hou FJ et al. ELCA in a severe coronary ostium lesion

Figure 1 Intravascular ultrasonography findings. A–D: Intravascular ultrasonography (IVUS) was performed after the laser catheter passed through the lesion and severe calcifications were noted; E and F: The laser catheter was slowly passed through the lesion and the stent was placed at 12 atm; G–J: The final IVUS findings showed no apparent dissection, malapposition, or underexpansion.

At the ostium lesions as compared to rotational atherectomy, it may be used as an alternative in the following cases: Thrombus, severe tortuosity, bifurcation, ostial coronary artery dissection, the failure of a Rotawire to pass through the target lesion, and severe heart failure. We successfully treated a severe calcified coronary ostium lesion by ELCA and small balloon dilatation. Nevertheless, further studies are needed to evaluate the efficacy and safety of ELCA vs rotational atherectomy.
CONCLUSION

Alternative use of ELCA and small balloon dilatation appears to be a safe and effective means of managing severely calcified coronary ostium lesions.

REFERENCES


Comprehensive management of malocclusion in maxillary fibrous dysplasia: A case report

Harneet Kaur, Sujata Mohanty, Gulsheen Kaur Kochhar, Shahid Iqbal, Anjali Verma, Ritasha Bhasin, Anuraj Singh Kochhar

**Abstract**

**BACKGROUND**

Fibrous dysplasia (FD) is a developmental hamartomatous bone disease characterized by a blend of fibrous and osseous entities. Though rarely malignant, the tumor can vary from being small and asymptomatic, to a fairly large sized lesion, progressing gradually, compromising occlusion and facial esthetics. Treatment approach depends on the stage of skeletal maturity. It primarily involves surgical management for stabilizing the disease process. Post-surgical comprehensive dental treatment is necessary for restoring form and function of the jaws and teeth. This article describes comprehensive orthodontic management of severe malocclusion in a surgically operated case of FD maxilla.

**CASE SUMMARY**

A 19-year female presented with a chief complaint of excessive gingival display when smiling. Dental history included swelling of gums around the upper right front teeth, diagnosed at the age of 15 as FD of the right anterior maxillary segment and treated with surgical recontouring of the dysplastic bone. The
INTRODUCTION

Fibrous dysplasia (FD) is a rare slow-growing disorder of the bone characterized histologically by excessive cellular fibrous connective tissue interspersed with irregular bony trabeculae[1,2]. Lichtenstein and Jaffe first identified and named this pathological bone deformity in 1938. The etiology is still unclear, although certain studies highlight mutations in the alpha-subunit of the stimulatory G protein encoded by the gene GNAS[3]. This rare clinical entity presents in three forms- monostotic, polyostotic, and polyostotic with endocrinopathies with hyperpigmentation (café-au-lait macules) known as McCune Albright syndrome[4]. Generalized FD involving the face and skull and appearing prominently in the middle third of the face is known as "Leontiasis ossea"[5]. Monostotic forms are less severe, most commonly involving the zygomatic-maxillary complex. In monostotic forms involving the jaw, the symptoms may vary depending on the location, resulting in malocclusions, asymmetry, facial deformity, nasal obstruction, visual changes, pain and/or paresthesia. Either crowding or spacing may be seen, because teeth positions can change following the contours of the bony deformity. Polyostotic FD presents as multiple lesions involving adjacent bone. Skeletal deformities in the extremities may be seen, due to repeated fractures in the affected bone[4]. The most common dental anomalies associated with FD include tooth rotation, oligodontia, displacement, enamel hypoplasia, enamel hypomineralization, taurodontism, retained deciduous teeth and attrition[6]. The differential diagnosis for FD includes ossifying fibroma, hyperparathyroidism, chronic osteomyelitis, Paget's disease, osteosarcoma and various other bony lesions. These entities should be excluded by taking a detailed history, evaluating the pattern of growth of clinical and radiological examinations showed adequate post-surgical healing. The surgically treated dysplastic area presented with right canting of the maxillary anterior occlusal plane. The maxillary teeth were torqued palatally, with the root of the right maxillary canine exposed clinically. We discuss sequential management of the associated malocclusion with comprehensive fixed orthodontics, along with special precautions taken to prevent reactivation of the quiescent and healed lesion.

CONCLUSION

The adequate healing of fibro-dysplastic bone post-surgery must be allowed before initiating orthodontic tooth movement in the dysplastic bone. Periodic follow-ups are needed to monitor stability of occlusion and any relapse of the lesion.

Key Words: Craniofacial fibrous dysplasia; Malocclusion; Orthodontic tooth movement; Jaw surgery; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This article discusses comprehensive management of severe malocclusion in a surgically treated case of maxillary fibrous dysplasia. Adequate healing of the fibro-dysplastic bone post-surgery must be allowed before initiating orthodontic tooth movement. Orthodontic treatment in such patients should mainly focus on improving function and esthetics. Special precautions must be taken to prevent reactivation/relapse of the quiescent/healed lesion, including sequential orthodontic tooth movement, lighter forces, and avoidance of direct orthodontic forces to the latent bone. Periodic follow-ups are necessary to monitor long-term stability of occlusion and any progression of the lesion.
the lesion, clinical examination, radiographs and histological analysis[6-8].

Management of FD depends upon the severity and rate of progression of the lesion. There are no accepted medical treatments for curing or stopping the progression of the disease. Bisphosphonates may be used for pain management, although they have shown no significant effect on disease progression[9]. Monoclonal antibodies to the receptor activator of nuclear factor kappa-B ligand and interleukin-6 have also been explored as a medical treatment for FD, resulting in reduction in bone pain, tumor growth, and bone turnover markers[10,11]. Most FD lesions require surgical management, mostly involving a conservative recontouring of the dysplastic bone to restore the normal bone shape. However, the need for re-surgery is high with this type of conservative surgical treatment. Reconstruction may be necessary for larger lesions [12]. The correction of concomitant malocclusion is also necessary, with the main focus on improving function and esthetics.

A thorough search revealed little mention of fibrous dysplasia in the orthodontic literature, and it is probably rarely seen in the typical orthodontic practice. There is limited information regarding protocols and precautions for orthodontic management of such lesions[13]. The case report follows and adheres to the CARE guidelines[14]. In the present article, we shall describe sequential dental and orthodontic management of malocclusion in a case of surgically treated FD of the maxilla.

CASE PRESENTATION

Chief complaints
A 19-year-old Indian female presented with a chief complaint of excessive display of gums when smiling.

History of present illness
Dental history included a hard, non-tender swelling of gums around the upper right canine-premolar teeth, first noted at 15 years of age. Orthopantomogram (OPG) X-ray revealed a mixed radiolucent/radiopaque lesion with ground-glass appearance, blending into the adjacent normal bone. There was loss of lamina dura of the associated teeth. Biopsy revealed trabeculae of mature bone with osteocytes in lacunae and rimmed by osteoid. The connective tissue was cellular and vascular, suggestive of a hamartomatous fibro-osseous lesion. The case was thus diagnosed as FD of the maxillary right anterior segment (Figure 1).

History of past illness
There was no significant medical, family and psychosocial history.

Personal and family history
There was no special personal and family history.

Imaging examinations
OPG X-ray revealed that the bone around the right maxillary canine-premolar teeth was less dense than in other areas, yet the bone pattern was regular. These findings suggested normal healing post-surgical resection. The lateral cephalometric analysis confirmed the aforementioned clinical diagnosis-Class II skeletal pattern, retrognathic mandible, retroclined maxillary anterior teeth and a normal growth pattern (Figure 2).

Extra-oral examination
The patient presented with symmetrical mesoprosopic face, competent lips, everted upper lip on right side, mild class II skeletal pattern with retrusive mandible and deep mentolabial sulcus. On smiling, inadequate display of incisor teeth with excessive gingival display on the right side was noted (Figure 2). Photographic analysis revealed canting of the inter-commissural line with respect to the inter-pupillary line, indicating an altered lip posture secondary to dysplasia and its surgical treatment (Figures 2 and 3A). Also, the photographs revealed no tooth display in the affected quadrant when smiling (Figure 3C).

Intra-oral examination
Intra-oral examination showed that the bony alveolus in the right maxillary canine-premolar region was markedly enlarged. The crowns of anterior maxillary teeth in this area were torqued lingually, with the root of the right maxillary canine (tooth #13)
being exposed clinically. The maxillary anterior occlusal plane was canted towards the right side, resulting in asymmetric anterior arch form. Mandibular teeth were well aligned and upright on basal bone. Both left and right buccal segments had Class I occlusion.

**MULTIDISCIPLINARY EXPERT CONSULTATION**

In the first phase of treatment, surgical recontouring of the dysplastic area was performed was done by the oral surgeons. Four years after surgery, when the lesion was resolved and adequate bone healing was achieved, the case was referred for second phase treatment involving correction of the residual malocclusion and restoration of smile esthetics.

This phase involved a comprehensive orthodontic treatment and was commenced after thorough clinical and radiographic examination.

**FINAL DIAGNOSIS**

FD of the maxillary right anterior segment.

**TREATMENT**

*Treatment plan*

The treatment objectives included endodontic management of the clinically exposed root apex of right maxillary canine #13 (Federation Dentaire Internationale notation), followed by orthodontic correction of the following: the palatal root torque of teeth in the right maxillary anterior segment; the cant of the maxillary anterior occlusal plane towards the right side; the excessive gingival display on the right side; and the excess overbite. The radiographic findings suggested adequate healing of the lesion four years after surgery, therefore we decided to initiate tooth movement of the displaced teeth.
**Figure 2 Post-surgical/pre-treatment photographs (October 2013).** A: Extra-oral frontal view; B: Extra-oral frontal with smile view; C: Extra-oral right profile view; D: Extra-oral right three-quarter view; E: Intra-oral right buccal view; F: Intra-oral front view; G: Intra-oral left buccal view; H: Intra-oral maxillary occlusal view; I: Intra-oral mandibular occlusal view; J: Orthopantomogram X-ray; K: Lateral cephalogram.

**Therapeutic intervention**

The treatment commenced with non-surgical endodontic treatment of the right maxillary canine #13, followed by apicoectomy of the clinically exposed root apex. Three months later, after confirming adequate healing, the orthodontic treatment was started using .022X.028” slot, conventional straight-wire mechanics. (Figure 4). Following alignment of the maxillary arch, .019X.025” stainless steel wire was placed with anterior differential palatal root torque (Figure 4A). Additional trans-palatal arch allowed cross-arch stabilization. After desired up righting of teeth was achieved, the remaining mandibular arch was bonded for alignment along with an asymmetric anterior intrusion in the upper arch using a unilateral intrusion arch made from .018” A.J. Wilcock archwire (Figure 4B). Then, a separate canine intrusion spring (again made from .018” A.J. Wilcock archwire) and continued asymmetric anterior intrusion were used to further correct the occlusal cant and anterior deep bite (Figure 4C). After adequate bite opening and levelling of the occlusal cant, post-intrusion finishing and detailing was done using .019X.025” stainless steel wire with artistic positioning bends (Figure 4D). OPG X-rays were taken periodically throughout the active tooth movement phase to monitor for any changes in bone morphology. The case was debonded after 41 mo of active treatment (Figure 5). A maxillary Essix retainer and mandibular bonded lingual retainer were placed to maintain the achieved dental corrections.
OUTCOME AND FOLLOW-UP

Periodic follow-ups were done every 6-mo for monitoring the stability of occlusion and any progression of the lesion. At the 3-year follow up, the patient's occlusion was stable and treatment results were well maintained without any signs and/or symptoms of an active lesion, despite discontinuing the maxillary retainer after two years (Figure 6).

DISCUSSION

FD is a type of bone disorder mostly involving craniofacial bones. Lesions are twice as common in the posterior maxilla as compared to the mandible[15]. Maxillary FD is associated with metabolic dysfunction and disordered bone architecture, which in turn affects tooth development and eruption.

The most common dental anomalies associated with FD include tooth rotation, oligodontia, displacement, enamel hypoplasia, enamel hypomineralization, impacted teeth and/or severe malocclusion[16]. The patient in the current report presented for esthetic reasons with excessive gingival display and malocclusion following surgically corrected/recontoured FD of the right maxilla in the canine-premolar area. The lesion resulted in crowding, rotations and displacement of teeth in the same quadrant, along with excessive palatal crown torque/buccal root torque of teeth, exposed root of the right maxillary canine tooth #13 and a canted occlusion plane. Deposition of dysplastic bone caused expansion of the buccal cortical plate, and surgical recontouring of the lesion caused exposure of the maxillary right canine root apex. It was treated by root canal treatment and apicoectomy. Our ultimate goal was to correct malocclusion by movement of teeth in the affected area.

FD in the craniofacial skeleton and related structures results in significant dysmorphic features like facial asymmetry and deformity. In the present case, characteristic features of FD were apparent on pre-surgical panoramic radiographs, described as a mixed radiolucent/radiopaque lesion with ground glass appearance[1-4]. Few articles have reported adequate healing of fibro-dysplastic bone following orthognathic surgery[17,18]. There is also very limited information regarding
orthodontic tooth movement in dysplastic bone, and the long-term prognosis of such treatment. A case report describing orthodontic repositioning of an impacted cuspid in fibro-dysplastic maxillary bone of a 12-year-old girl suggests a normal response of dysplastic bone to orthodontic forces[19]. Lee et al[2] and Akintoye et al[20] suggest delaying orthodontic therapy until after the age of skeletal maturity, based on the individual patient’s needs and findings from an initial orthodontic evaluation. The advantage of such delay is that FD disease activity tends to decrease after skeletal maturity, which is reflected in a decline in bone turnover markers, a decrease in the number of mutated skeletal stem/progenitor cells, and a tendency of FD histology to improve over time[21]. Orthodontic treatment for the patient in the current report was initiated after completion of the pubertal growth spurt. Furthermore, four years postsurgery, there were no signs and/or symptoms of an active lesion. The OPG X-ray revealed less osseous density but predominantly regular woven bone in the area of the lesion, indicative of successful healing.

A position correlation between increase in c-fos gene and FD was described by Marie et al[22]. Increase in c-fos gene has been related to post-traumatic FD in a couple of case reports[23,24]. Therefore, to avoid the risk of transforming a quiescent lesion into an aggressively growing lesion, we planned to proceed with sequential orthodontic tooth movement, using light forces, without applying any direct forces to the bone (through micro-implants) and to monitor the lesion periodically. There were no signs of reactivation of the FD lesion during the active orthodontic treatment period of 41 mo, as evident on post-operative photographs and radiographs (Figure 5), which may be attributed to the following special precautions taken in this case: Delaying orthodontic treatment until adequate healing of the surgically treated bone was confirmed, as well as skeletal maturity was attained[21]; Sequential orthodontic mechanics: Initial torquing and up righting of the teeth was followed by segmental intrusion of anterior teeth to correct the cant of the occlusal plane; Use of light forces: To correct the anterior cant of the occlusal plane, a unilateral cantilever intrusion arch was used for unilateral intrusion of the right maxillary incisors. The forces were kept light, below 20gms, and 0.018” A.J Wilcock wire was used instead of conventional 0.017x0.25” TMA wires. Additionally, we did a separate intrusion for the right maxillary canine; Avoid direct forces to the healed bone: We avoided using micro-implants for supported intrusion, to prevent any immediate trigger for reactivation of the lesion.
The total duration of active treatment was 41 mo. This is in accordance with previous studies showing that orthodontic treatment duration is increased in FD cases [3,20]. Using light forces over longer duration also minimizes the possibility of relapse after orthodontic treatment. There is limited data on long-term outcomes of orthodontic treatment and the effectiveness of retention in FD cases[3,13]. Therefore, we proposed long-term retention in the present case. Maxillary Essix retainer and mandibular bonded lingual retainer were given to maintain the achieved dental corrections. Periodic follow-ups were done every 6-mo. The 3-year follow-up records showed relatively stable occlusion and minimal relapse, despite discontinuing the maxillary retainer after two years. However, the authors believe that results from this case report may not be applicable to all patients with FD and further characterization of orthodontic management should be decided by more precise, prospective clinical studies.

CONCLUSION

In this report, FD of the maxilla was successfully treated with surgical recontouring and orthodontic treatment. The goal of orthodontic treatment in FD affecting the maxillary region is to focus on improving function and esthetics, while avoiding reactivation of the quiescent/healed lesion. Adequate healing of fibro-dysplastic bone post-surgery must be allowed before commencement of orthodontic tooth movement, as inferred from a good outcome in this case. Special precautions must be taken, such as sequential orthodontic tooth movement, use of lighter forces and avoidance of direct orthodontic forces to the latent bone. Periodic follow-ups are necessary to
Figure 6 Three years post-retention pics (December 2020). A: Extra-oral frontal view; B: Extra-oral frontal with smile view; C: Extra-oral right profile view; D: Extra-oral right three-quarter view; E: Intra-oral right buccal view; F: Intra-oral front view; G: Intra-oral left buccal view.

To monitor the stability of occlusion and any relapse of the lesion.

ACKNOWLEDGEMENTS

We acknowledge the patient and her parents for providing us with consent to perform the treatment, being cooperative throughout the treatment and follow-ups, and giving us permission to submit and publish the records for this article. We also acknowledge Dr. Verma P (DDS, MS, FAGD, Diplomate, American Board of Endodontics) for the prompt professional guidance and expertise to polish the manuscript further.

REFERENCES

1. Costanzi MA, Velasco e Cruz AA. Envolvimento orbitário difuso por dysplasia fibrosa na síndrome de McCune Albright: Relato de caso. Arq Bras Oftalmol 2007; 70: 1021-1023
Kaur H et al. Orthodontic management of maxillary fibrous dysplasia

1747-1749 [PMID: 26070936 DOI: 10.1093/rheumatology/kev221]


Intravascular papillary endothelial hyperplasia as a rare cause of cervicothoracic spinal cord compression: A case report

Hong-Lin Gu, Xiao-Qing Zheng, Shi-Qiang Zhan, Yun-Bing Chang

BACKGROUND
Intravascular papillary endothelial hyperplasia (IPEH) is a rare benign reactive vascular lesion that grows into an expansile compressing mass. It most commonly involves the skin and subcutaneous tissue. Spinal involvement is rare, with only 11 reported cases in the literature. We report, to our knowledge, the first case of IPEH in the cervicothoracic spinal canal and present a literature review.

CASE SUMMARY
A 27-year-old man presented with acute-onset neck pain, numbness, and weakness in his extremities. Magnetic resonance imaging showed an epidural mass in the cervicothoracic (C6-T1) spinal canal and vertebral hemangioma (VH) involving the C7 vertebral body. C6-T1 Laminectomy and radical excision of the mass were performed. Histopathological examinations revealed papillary proliferation of vascular endothelial cells with thrombus formation, and an IPEH diagnosis was made. By his 6-mo follow-up appointment, his symptoms were relieved without recurrence. The possible pathogenesis, clinical and imaging features, differential diagnosis, and management of IPEH were reviewed.

CONCLUSION
We report, to our knowledge, the first case of IPEH in the cervicothoracic spinal canal, treated via complete resection, and showing a favorable outcome. We found a causal relationship between spinal IPEH and VH; this partly explains the mechanism of IPEH.

Key Words: Intravascular papillary endothelial hyperplasia; Cervicothoracic; Spinal cord compression; Thrombosis; Hemangioma; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
Intravascular papillary endothelial hyperplasia (IPEH) is a rare benign reactive vascular lesion that grows into an expansile compressing mass. Spine involvement is rare, with only 11 case reports on its occurrence. We reported the first case of IPEH in the cervicothoracic spinal canal, which was treated via complete resection and had a good prognosis. We also found a causal relationship between spinal IPEH and vertebral hemangioma, and this partly explained the mechanism of IPEH.

**Core Tip:** Intravascular papillary endothelial hyperplasia (IPEH) is a rare benign reactive vascular lesion that grows into an expansile compressing mass. Spine involvement is rare, with only 11 case reports on its occurrence. We reported the first case of IPEH in the cervicothoracic spinal canal, which was treated via complete resection and had a good prognosis. We also found a causal relationship between spinal IPEH and vertebral hemangioma, and this partly explained the mechanism of IPEH.

**Citation:** Gu HL, Zheng XQ, Zhan SQ, Chang YB. Intravascular papillary endothelial hyperplasia as a rare cause of cervicothoracic spinal cord compression: A case report. World J Clin Cases 2021; 9(34): 10681-10688

**URL:** https://www.wjgnet.com/2307-8960/full/v9/i34/10681.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v9.i34.10681

**INTRODUCTION**

Intravascular papillary endothelial hyperplasia (IPEH) was first reported in 1923 by Pierre Masson in a case of an infected hemorrhoidal vein. Initial reports referred to the lesion as a “Masson tumor” or hemangioendotheliome vegetant intravasculaire[1]. In 1975, Clearkin and Enzinger described the lesion as an unusual and exaggerated thrombus reorganization, rather than a true tumor, and the condition was renamed IPEH[2]. IPEHs typically occur in the skin and subcutaneous tissues of the head and neck or limbs[3]; it rarely occurs in the spine. To our knowledge, only 11 cases of IPEH of the spine have been reported. We report the first case of IPEH of the cervicothoracic spinal canal and present a literature review.

**CASE PRESENTATION**

**Chief complaints**
A 27-year-old man presented to the Department of Spine Surgery of our hospital with complaints of neck pain, limb numbness, and weakness.

**History of present illness**
His symptoms started suddenly, 4 d prior to hospital presentation.

**History of past illness**
The patient had no trauma history. A similar episode of transient limb numbness and weakness occurred 6 years earlier.

**Personal and family history**
He denied any personal or family history of other diseases.

**Physical examination**
Physical examination revealed tenderness of the paraspinal muscle of the C6-T1 spinous process, muted sensory responsiveness to touch along the T1 dermatome, and grade IV muscle strength in the four limbs.

**Laboratory examinations**
The results of all blood analyses — including coagulation markers, inflammatory indicators, and tumor markers — were within normal limits.

**Imaging examinations**
Spinal radiography and computed tomography demonstrated no obvious bone destruction. Enhanced cervical magnetic resonance imaging (MRI) showed a homogenously enhanced epidural mass in the C6-T1 spinal canal. The mass compressed the spinal cord and extended into the left C7-T1 foramen. It appeared hypointense on T1-weighted images (T1WIs) and hyperintense on T2WI. Moreover, a 0.5 cm × 0.5 cm × 0.6 cm-sized heterogeneously enhanced hyperintense mass was...
found in the C7 vertebral body on T2WI, which was suggestive of a benign vertebral hemangioma (VH) (Figure 1).

**DIFFERENTIAL DIAGNOSIS**
The mass was possibly an epidural schwannoma; however, we needed to exclude a nonneurogenic tumor diagnosis. The patient required surgical spinal cord decompression for symptom relief. The final diagnosis was confirmed histopathologically.

**FINAL DIAGNOSIS**
The final diagnosis was cervicothoracic spinal IPEH.

**TREATMENT**
The patient underwent C6-T1 Laminectomy, left C7-T1 foramen decompression, and radical excision of the epidural mass. A C6-T1 posterior instrumented fusion was performed to stabilize the facetectomy at the spinal level, proximal to the cervicothoracic junction. We observed a dark red, nodular, highly vascularized 3 cm × 1.5 cm × 1 cm mass compressing the spinal cord and left C7 nerve root dorsally. The mass was subsequently excised (Figure 2), and an intraoperative frozen section revealed a diagnosis of benign neoplasm originating from blood vessels. Histopathological examination revealed papillary proliferation of vascular endothelial cells with thrombus formation, consistent with IPEH (Figure 3).

**OUTCOME AND FOLLOW-UP**
After the surgery, the patient showed gradual neurologic improvement. At his 6-mo follow-up, he was symptom-free, with no spinal cord compression or recurrence on MRI (Figure 4). The clinical timeline of the patient is depicted in Figure 5.

**DISCUSSION**
IPEH is a rare benign reactive vascular lesion that expands to form a compressing mass. There is no age predilection for IPEH, and its incidence is higher in women than in men\(^4\), with a female-to-male ratio of 4:1 for intracranial lesions\(^5\). Although spinal presentations are rare, they occur more commonly in men\(^6\). IPEHs are commonly located in the skin and subcutaneous tissues of the head and neck or limbs\(^3\) but have also been reported in the oral mucosa, lip, thyroid, maxillary sinus, parotid, lung, superior vena cava, adrenal gland, renal vein, forearm, foot, and intracranially\(^7-11\). There are 11 reported cases of spinal IPEH, including ten cases involving men and one case involving a woman, with patient age ranging from 16 years to 58 years (see Table 1 for details)\(^6,12-21\). Among these cases, in one case, the mass was located in the vertebral body and in the remaining ten cases, the mass was located in the spinal canal. Only one case of an intradural mass and nine cases of an epidural mass have been reported. The most common site of involvement was the thoracic spinal canal (\(n = 7\)). Of the three remaining cases, two cases involved the lumbar spine and one case involved the thoracolumbar junction. The mass in one case was multifocal, involving the cervical, thoracic, and lumbar vertebral bodies. The present report is the first report of cervicothoracic spinal IPEH.

The pathogenesis of IPEH remains controversial. Some authors believe that IPEH is an excessive reaction to a normal thrombus reorganization process\(^2,22-24\). Others proposed that IPEH is a benign proliferation of endothelial cells with secondary thrombosis and fibrin deposition\(^25\). Few authors believe that there is a causal relationship between VH and spinal IPEH. Mozhdehipanah et al\(^17\) reported a case of IPEH in the T4-T6 spinal canal. Two adjacent vertebral bodies (T4 and T5) demonstrated VH. The author speculated that bleeding within the spinal canal
<table>
<thead>
<tr>
<th>No.</th>
<th>Ref.</th>
<th>Year</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Primary location</th>
<th>Clinical features</th>
<th>Radiological Features</th>
<th>Treatment</th>
<th>Size (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Porter et al [14]</td>
<td>1995</td>
<td>16</td>
<td>M</td>
<td>T6 posterior epidural mass</td>
<td>Midthoracic-radicular back pain with hesitancy for 1-wk duration</td>
<td>CT myelography: extradural thecal compression posteriorly with abnormal lamina</td>
<td>T6 laminectomy with T5-T6 right partial facetectomy</td>
<td>4 × 2 × 1</td>
</tr>
<tr>
<td>3</td>
<td>Taricco et al [15]</td>
<td>1999</td>
<td>17</td>
<td>M</td>
<td>T12-L1 posterior epidural mass</td>
<td>Pain, numbness, paresis of left lower limb with bladder dysfunction for 1 mo</td>
<td>Contrast-enhanced CT of spine: hyperdense lesion; MRI: T1-isointense, T2-hyperintense with homogeneous contrast enhancement</td>
<td>T12-L1 laminectomy with radical excision of mass</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>4</td>
<td>Petry et al [12]</td>
<td>2009</td>
<td>47</td>
<td>M</td>
<td>Multifocal lesions of the spine</td>
<td>Diffuse low back pain</td>
<td>MRI T1-isointense, T2-hyperintense with homogeneous contrast enhancement</td>
<td>No surgery</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>5</td>
<td>Lanotte et al [16]</td>
<td>2010</td>
<td>33</td>
<td>M</td>
<td>T6-T7 paravertebral mass extending epidural space</td>
<td>Back pain, hesitancy with paraparesis for 2 wk</td>
<td>MRI T1 hypo-intense, T2 hyperintense mass</td>
<td>T6 laminectomy and excision of intracanal mass</td>
<td>4.5 × 2.5 × 2.5</td>
</tr>
<tr>
<td>6</td>
<td>Mozhdahi-panah et al [17]</td>
<td>2013</td>
<td>58</td>
<td>M</td>
<td>T4-6 posterior epidural mass</td>
<td>Spastic paraparesis and sensory deficit for 1 mo</td>
<td>MRI T2 hyperintense mass</td>
<td>Laminectomy and radical excision of mass</td>
<td>3×1</td>
</tr>
<tr>
<td>7</td>
<td>Bhalla et al [21]</td>
<td>2013</td>
<td>51</td>
<td>F</td>
<td>L1 centered on spinous process and involving pedicles</td>
<td>Back pain with paraparesis</td>
<td>MRI L1 centered on spinous process and involving pedicles causing cauda equina compression with central hypointensity on T2-weighted MRI</td>
<td>Preoperative embolization, incomplete excision and Radiotherapy</td>
<td>4.6×4.3×5.5</td>
</tr>
<tr>
<td>8</td>
<td>Singla et al [18]</td>
<td>2016</td>
<td>40</td>
<td>M</td>
<td>T12-L1 dumbbell-shaped mass</td>
<td>Back pain and numbness of the right lower trunk for 2 yr</td>
<td>MRI dumbbell-shaped mass mimicking schwannoma</td>
<td>Radical excision</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>9</td>
<td>Behera et al [19]</td>
<td>2017</td>
<td>32</td>
<td>M</td>
<td>T4-5 posterior epidural mass</td>
<td>Paraplegia for 4 mo</td>
<td>MRI T1 hypo-intense, T2 hyperintense mass</td>
<td>Radical excision</td>
<td>5 × 3 × 2</td>
</tr>
<tr>
<td>10</td>
<td>Tanaka et al [20]</td>
<td>2018</td>
<td>40</td>
<td>M</td>
<td>L2-3 intradural mass</td>
<td>Low back pain and leg pain beginning approximately 5 yr ago and 1 mo ago</td>
<td>Isointense on T1 and hypointense with partial areas of high signal intensity on T2 without contrast enhancement</td>
<td>L2-3 laminectomy and durotomy with complete excision of mass</td>
<td>2.5 × 1.5 × 1</td>
</tr>
<tr>
<td>11</td>
<td>Oktar et al [21]</td>
<td>2019</td>
<td>37</td>
<td>M</td>
<td>T4-5 dumbbell-shaped mass</td>
<td>Dermatomal tingling burning pain with paresis of right lower limb for 1 mo</td>
<td>MRI dumbbell-shaped mass mimicking schwannoma</td>
<td>Radical excision</td>
<td>5 × 2 × 3</td>
</tr>
<tr>
<td>12</td>
<td>Present case</td>
<td>2020</td>
<td>27</td>
<td>M</td>
<td>C6-T1 posterior epidural mass</td>
<td>Neck pain and numbness of the extremities</td>
<td>MRI: T1-hypointense, T2-hyperintense with homogeneous contrast enhancement</td>
<td>C6-T1 laminectomy with C7-T1 left partial facetectomy and radical excision of the mass</td>
<td>3 × 1.5 × 1</td>
</tr>
</tbody>
</table>

MRI: Magnetic resonance imaging; CT: Computed tomography.
Figure 1 Preoperative magnetic resonance imaging. A and D: Sagittal T2-weighted imaging (T2WI); B: Sagittal T1-weighted imaging (T1WI); C: Sagittal T1WI of the spine with contrast; E: Axial T2WI; F: Axial T1WI with contrast. A posterior spinal epidural mass located from C6 to T1 (thin arrow) appeared high signal intensity on T2WI sagittal and axial images, and low signal intensity on T1WI images. A gadolinium-enhanced scan reveals inhomogeneous enhancement. And a 0.5 cm × 0.5 cm × 0.6 cm-sized round tumor (thick arrow) can be seen on the left side of the C7 vertebral body; high signal intensity is observed on T2WI and homogeneous enhancement is detected on T1WI after contrast agent administration.

Figure 2 Intraoperative images. A: Operative view of a dark red, nodular, highly vascularized epidural mass (thick arrow) measuring 3 cm × 1.5 cm × 1 cm compressing the left side of the spinal cord (thin arrow) after C6-T1 Laminectomy. B: View of the surgeon after complete resection of the mass and decompression of dura (thin arrow) and left C7 nerve root (triangle). C: Nodular fragment of the lesion.

IPEH mostly exhibited isointensity or low signal intensity on T1WI and high or variable signal intensity on T2WI with contrast enhancement. Three cases presented as dumbbell-shaped masses, mimicking schwannoma[6]. The present patient was preoperatively diagnosed with epidural schwannoma, which typically features papillary proliferation of vascular endothelial cells, localized intravascularly, with normal thrombus formation in the entire papillary tissue[4,23,26]. The pathological findings in our case are consistent with a diagnosis of IPEH. However, IPEH must be
Figure 3 Histological features of the epidural mass. A: Hematoxylin-eosin (HE); × 100; B: HE × 200. Histopathological pictomicrograph shows dilated thin-walled vessels lined by a monolayer of obese endothelial cells (thin arrows). The lumen appears to be filled with organizing thrombi (thick arrow).

Figure 4 Postoperative magnetic resonance imaging at 6-mo follow-up. A-C: Magnetic resonance imaging showing total relief of the previously noted spinal cord compression and no signs of recurrence.

Figure 5 Patient timeline. MRI: Magnetic resonance imaging; IPEH: Intravascular papillary endothelial hyperplasia.

distinguished from other benign and malignant lesions, including cavernous/capillary hemangioma, Kaposi sarcoma, endovascular papillary, and angioendothelioma. Importantly, IPEH should be differentiated from angiosarcoma to avoid unnecessary radiation and surgery[11].
Spinal manifestations of IPEH may be associated with chest or back pain, lower limb numbness, paralysis, and bladder dysfunction caused by spinal cord or cauda equina compression[6]. Treatment is only considered when pain or compression-related symptoms occur, and complete surgical resection is the preferred treatment. Prognosis after complete resection is good, with minimal recurrence. Nine of the 11 patients in the reported cases underwent radical resection, and no recurrence was noted during follow-up. Further, the patient in the present case—who presented with acute-onset numbness and weakness of the limbs owing to spinal cord compression—underwent complete surgical resection. His symptoms were relieved and had not recurred by the 6-mo follow-up visit. Adjuvant radiotherapy can be considered for lesions that cannot be completely removed or that are recurrent. To our knowledge, there is only one reported case of radiotherapy for incompletely resected spinal IPEH. This case showed the potential benefit of radiation following the recurrence of benign IPEH in a patient with epidural disease[21].

CONCLUSION

The main pathological change attributable to IPEH is benign vascular endothelial papillary hyperplasia with thrombosis; however, the mechanism of this relationship remains controversial. Spinal IPEH is rare, occurring more frequently in men, and is localized to the thoracic spine. Importantly, our findings suggest that spinal IPEH is related to VH. There are no prior reports of IPEH in the cervical spinal canal. To our knowledge, this is the first case of IPEH in the cervicothoracic spinal canal which was associated with a favorable outcome after complete resection.

ACKNOWLEDGEMENTS

The authors wish to thank the patient for his contributions to this report.

REFERENCES


Proximal true lumen collapse in a chronic type B aortic dissection patient: A case report

Li Zhang, Wei-Kang Guan, Hua-Ping Wu, Xiang Li, Kai-Ping Lv, Cun-Liang Zeng, Huan-Huan Song, Qian-Ling Ye

ORCID number: Li Zhang 0000-0002-8229-9493; Wei-Kang Guan 0000-0002-6527-8930; Hua-Ping Wu 0000-0001-9675-7400; Xiang Li 0000-0002-7900-3022; Kai-Ping Lv 0000-0001-9167-0998; Cun-Liang Zeng 0000-0002-0203-9844; Huan-Huan Song 0000-0003-1955-0822; Qian-Ling Ye 0000-0001-7601-7210.

Author contributions: Wu HP, Zhang L, Li X and Lv KP were responsible for the treatment and management of the patient; Song HH and Zeng CL contributed to data collection, literature review, and manuscript writing; Guan WK and Ye QL analyzed the data of the patient; All authors were involved in writing the manuscript and 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 conflict of interest to disclose.

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).

Abstract

BACKGROUND
In the context of aortic dissection, increasing pressure within the newly formed false lumen can result in the progressive compression of the true aortic channel. However, true lumen collapse in chronic type B aortic dissection (cTBAD) patients is rare, with few clinical or experimental studies to date having explored the causes of such collapse.

CASE SUMMARY
In the present report, we describe a rare case of true-lumen collapse in an 83-year-old patient diagnosed with cTBAD, and we discuss potential therapeutic interventions for such cases. Following thoracic endovascular aortic repair (TEVAR), computed tomography angiography revealed satisfactory stent-graft positioning, no endoleakage, true lumen enlargement, thrombus formation in the false lumen, and slight enlargement of the true lumen distal to the stent-graft. Computational hemodynamic analyses indicated that the wall shear stress and pressure within the false lumen were significantly reduced following TEVAR.

CONCLUSION
TEVAR treatment of cTBAD patients suffering from proximal true lumen collapse can facilitate some degree of effective remodeling.

Key Words: True lumen collapse; Chronic type B aortic dissection; Thoracic endovascular repair; Computational hemodynamics analysis; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
Core Tip: We describe a rare case of true-lumen collapse in an 83-year-old patient with chronic type B aortic dissection, and we discuss potential therapeutic interventions for such cases.

Citation: Zhang L, Guan WK, Wu HP, Li X, Lv KP, Zeng CL, Song HH, Ye QL. Proximal true lumen collapse in a chronic type B aortic dissection patient: A case report. World J Clin Cases 2021; 9(34): 10689-10695
URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10689.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10689

INTRODUCTION

Intimal aortic tears that ultimately cause aortic dissection can allow blood to flow between the medial layers of the dissected aorta, leading to the formation of a double-barreled aortic lumen. Over time, increasing pressure within the newly formed false lumen can result in the progressive compression of the true aortic channel. Studies in experimental model systems suggest that the incidence of true-lumen collapse is strongly dependent upon the differential between the inflow : outflow capacity ratios of the true lumen and the false lumen, with this incidence further being influenced by other physiologic and anatomic factors. The definitive treatment for such cases of true lumen collapse is the targeted repair of the entry tear as a means of reducing inflow into the false lumen.[1,2]. True lumen collapse in chronic type B aortic dissection (cTBAD) patients is rare, with few clinical or experimental studies to date having explored the causes of true lumen collapse in this context. Optimal treatment methods for patients suffering from this rare condition are similarly not well defined. In the present report, we describe the case of a cTBAD patient who suffered from true lumen collapse. Using computed tomography angiography (CTA) data from this patient collected at both initial presentation and at 3 and 28 mo post-treatment, we additionally develop computational models to observe hemodynamic changes before and after thoracic endovascular aortic repair (TEVAR).

CASE PRESENTATION

Chief complaints
An 83-year-old male was admitted to our hospital due to the incidental detection of an aortic dissection aneurysm during a standard health examination.

History of present illness
The patient did not exhibit any chest or back pain and was incidentally diagnosed with an aortic dissection aneurysm while undergoing a routine health evaluation.

History of past illness
The patient had previously been diagnosed with hepatic and renal cysts.

Personal and family history
The patient had no remarkable personal or family history.

Physical examination
The arteries of the extremities exhibited normal pulsatile activity, and all limbs exhibited normal motor and sensory functions. There was also no evidence of peritonitis.

Laboratory examinations
No abnormality.

Imaging examinations
CTA confirmed the dissection of the descending aorta and aortic arch. A dilated false
lumen with evidence of calcification was visible as was the collapse of the proximal true lumen. The aortic dissection had a maximal diameter of 51.8 mm, with no tearing of the thoracic aorta. The distal tear was located on the common trunk of the celiac axis and the superior mesenteric artery and had a maximal diameter of 10.71 mm (Figure 1).

**FINAL DIAGNOSIS**

CTBAD with proximal true lumen collapse, liver cyst, renal cyst.

**TREATMENT**

Significant compression of the proximal true lumen was evident in an aortogram, and the catheter used for this intervention had a helical shape (Figure 2A) that was corrected using a Lunderquist guidewire (Figure 2B). In order to achieve true lumen enlargement without causing endoleakage, upper limb ischemia, or stroke, we employed a left subclavian arterial fenestration approach to conduct TEVAR. Owing to differences in the diameter of the aortic arch and the descending aorta, we used two ANKURA® stent-grafts (Lifetech Scientific Co., Ltd., Shenzhen, China). These stent-grafts (34-30 mm and 30-26 mm diameter, 120 mm long) were deployed from the distal to the left common carotid artery to the descending aorta such that they overlapped one another. The sharpened end of a V18 wire was then used to fenestrate the ANKURA stent graft, with this hole being enlarged through the use of a balloon dilatation catheter (INVATEC 3.5-120 mm and 8-40 mm, Medtronic, Inc., Dublin, Ireland), after which we placed the Fluency stent (10 mm in diameter, 40 mm in length) into the ANKURA stent graft. Balloon dilatation of the stent-graft was then performed. Subsequent angiography did not show any evidence of endoleakage, with satisfactory left subclavian artery blood flow (Figure 2C and D). A Coda balloon (Cook Medical, Bloomington, IN, United States) was used to expand the aortic stent overlap, and the stent shape was satisfactory upon subsequent angiographic assessment (Figure 2E and F).

**OUTCOME AND FOLLOW-UP**

On day 5 post-treatment, the patient was discharged without any incidence of paraplegia, neurological abnormalities, or other serious adverse events. At 3- and 28-mo post-surgery, the patient underwent routine physical examination and CTA. CTA imaging data in the DICOM format were imported into the Mimics 19.0 software (Materialise Inc., Leuven, Belgium) for three-dimensional model reconstruction and associated measurements. Data produced by Stefanov et al.[3] were used to guide hemodynamic analyses of the cardiac cycle.

Following TEVAR, CTA results indicated that the true lumen was significantly enlarged in the stented region, while the false lumen gradually decreased in size and became completely thrombotic (Figure 3). These results thus indicate that following TEVAR the maximal descending aortic diameter grew smaller, whereas the diameter and area of the true lumen increased (Table 1).

Prior to TEVAR, flow within the false lumen exhibited helical features, and pressure and wall shear stress values were significantly higher in the false lumen relative to the true lumen, with these changes being most prominent in the enlarged region of the false lumen. Following TEVAR, there was no evidence of helical flow within the false lumen. In addition, treatment was associated with significant reductions in both pressure and wall shear stress within the false lumen and significant increases in these values in the true lumen, with these pressure values being nearly equal proximal to the tear (Figure 4).

**DISCUSSION**

Following the publication of the 2014 European Society of Cardiology guidelines[4], preemptive TEVAR has now received broad approval as the treatment of choice for patients diagnosed with subacute uncomplicated type B aortic dissection. Treatment of
Table 1 Aortic remodeling following thoracic endovascular aortic repair

<table>
<thead>
<tr>
<th>Time of Measurement</th>
<th>Maximal Diameter of Descending Aorta</th>
<th>Diameter and Area of the True Lumen at the Level of the 11th Thoracic Vertebra</th>
<th>Diameter and Area of the True Lumen at the End of the Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to TEVAR</td>
<td>51.8 mm</td>
<td>7.2/19.9 mm 119.6 mm²</td>
<td></td>
</tr>
<tr>
<td>3-mo post-treatment</td>
<td>50.8 mm</td>
<td>12.8/25.0 mm 265.0 mm²</td>
<td>16.8/27.0 mm 349.8 mm²</td>
</tr>
<tr>
<td>28-mo post-treatment</td>
<td>50.5 mm</td>
<td>14.8/25.5 mm 302.9 mm²</td>
<td>18.0/27.3 mm 376.9 mm²</td>
</tr>
</tbody>
</table>

TEVAR: Thoracic endovascular aortic repair.

Figure 1 Computed tomography angiography results prior to thoracic endovascular aortic repair. A: True lumen collapse (arrow); B: The maximal diameter of the distal tear was 10.71 mm; C: The maximal diameter of the descending aorta was 51.8 mm; D: Type III aortic arch, with the dissecting aneurysm being immediately adjacent to the left subclavian artery.

these patients is recommended in order to reduce the risk of aortic expansion, rupture, and recurrent dissection. Even following treatment, between 20% and 40% of these patients will need a secondary operation for the treatment of aortic aneurysmal degeneration[5]. Favorable aortic remodeling above the celiac artery has been observed following TEVAR treatment, with no differences in remodeling outcomes being observed between acute and chronic complicated type B aortic dissection patients[6]. Favorable early and mid-term outcomes have previously been observed following the endovascular treatment of type B chronic aneurysmal aortic dissection [7], and one or more additional procedures can achieve a good long-term result[8]. Secondary aortic intervention after TEVAR for type B aortic dissection does not affect survival[9]. Even so, these past findings suggest that endovascular treatment the TEVAR-based treatment of proximal true-lumen collapse in a cTBAD patient could be considered to be one of the effective treatment options. Following TEVAR, the false lumen in this patient gradually underwent complete thrombosis, the maximal descending aortic diameter decreased, and the size and diameter of the true lumen in both the graft and distal regions increased, consistent with the work of Chung et al[2]. For patients with symptomatic aortic dissection with true lumen collapse, endovascular fenestration of the dissection flap and/or expansion of the true lumen with a large-diameter balloon can be used to increase the perfusion of the true lumen, as demonstrated in previously published case reports[10,11].

Few anatomic predictors of true lumen collapse had been identified to date, with true lumen size at admission being the factor most strongly associated with such collapse or malperfusion, as it typically corresponds to significant changes in false lumen blood flow as measured via computational hemodynamic analyses[12]. Such computational hemodynamic approaches have been used with increasing frequency as a means of assessing cases of aortic dissection, as both pressure and wall shear stress are key parameters associated with dissection onset and progression. Importantly, lower levels of wall shear stress in the false lumen can promote local thrombosis[13]. In the present case, we observed high pressure within the proximal false lumen that was associated with an impinging jet of high-pressure blood flow along the outer wall of this false lumen. This jet impingement was also associated with a visible local increase in the aortic diameter. Following the TEVAR treatment of this patient, we
observed complete thrombosis of the false lumen with only a small percentage of blood flow still entering into this compartment. This was associated with higher pressure in the true lumen relative to the false lumen unlike the near-equal pressure values observed before treatment, thereby reversing this factor associated with luminal collapse. Prior to TEVAR, we observed clear evidence of higher shear wall stress in the proximal false lumen relative to the true lumen, whereas this was reversed following treatment. Our computational analyses further confirmed that reductions in pressure and wall shear stress may facilitate positive aortic wall remodeling.

While these findings are promising, this study is limited by the fact that it is a description of a single case. Future studies that expand upon these results in a larger patient cohort are essential in order to define more conclusively optimal treatment strategies in similar cases.
Figure 4 Computational hemodynamic analysis in the true and false lumen before and after thoracic endovascular aortic repair treatment.

A: Blood flow feature; B: Pressure; C: Wall shear.
CONCLUSION

The findings from the present case suggest that TEVAR can be effectively implemented as a means of treating proximal true-lumen collapse in cTBAD patients. This treatment strategy achieved good efficacy and was not associated with any significant neurological complications, stent-related complications, or other adverse events. Follow-up data from this patient indicated that TEVAR induced some degree of remodeling when used to treat CTBAD.

REFERENCES


Tigecycline sclerotherapy for recurrent pseudotumor in aseptic lymphocyte-dominant vasculitis-associated lesion after metal-on-metal total hip arthroplasty: A case report

I-Hao Lin, Chun-Hao Tsai

ORCID number: I-Hao Lin 0000-0003-0596-7723; Chun-Hao Tsai 0000-0002-4428-3132.

Author contributions: Tsai CH contributed to the study concept and design; Lin IH and Tsai CH performed data acquisition, Lin IH contributed to manuscript writing; Tsai CH critically revised manuscript, and Lin IH and Tsai CH gave final approval of the 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 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).

Country/Territory of origin: Taiwan

Specialty type: Surgery

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Abstract

BACKGROUND
Metal-on-metal (MoM) total hip arthroplasty (THA) has been associated with adverse reactions to metal debris, presenting clinically as pseudotumors.

CASE SUMMARY
This case report presents a female aged 73 year-old with MoM THA-related pseudotumor. After arthrotomy and bursectomy surgeries, histologic examinations of surgical specimens revealed a specific lymphocyte-dominant immunologic response, now known as aseptic lymphocyte-dominant vasculitis-associated lesion (ALVAL). Due to soft tissue persisting effusion after arthrotomy and bursectomy, revision surgery was then performed with ceramic-on-polyethylene THA. However, revision did not resolve the patient’s symptoms. Here we describe our application of tigecycline sclerotherapy to treat recurrent pseudotumor after revision THA and no recurrence after 24-mo follow-up.

CONCLUSION
Tigecycline sclerotherapy is safe and effective in the management of recurrent pseudotumor after revision non-MoM THA in ALVAL cases.

Key Words: Aseptic lymphocyte-dominant vasculitis-associated lesion; Metal-on-metal total hip arthroplasty; Pseudotumor; Tigecycline; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
Core Tip: Metal-on-metal (MoM) total hip arthroplasty (THA) often associates with metal debris, presenting as pseudotumors. We here described a case with MoM THA-related pseudotumor. Revision surgery was performed; however, further histologic examinations revealed the presence of aseptic lymphocyte-dominant vasculitis-associated lesion (ALVAL) and recurrent pseudotumors formation was noted after revision THA. We locally injected an infusion of tigecycline sclerotherapy for treating the pseudotumor successfully. Our findings indicated that tigecycline sclerotherapy is safe and effective in managing recurrent pseudotumor after revision non-MoM THA in ALVAL cases.

Citation: Lin IH, Tsai CH. Tigecycline sclerotherapy for recurrent pseudotumor in aseptic lymphocyte-dominant vasculitis-associated lesion after metal-on-metal total hip arthroplasty: A case report. World J Clin Cases 2021; 9(34): 10696-10701
URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10696.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10696

INTRODUCTION

Metal-on-metal (MoM) hip articulations were first introduced in the 1960s and were thought to be more favorable biologically and biomechanically than conventional metal-on-polyethylene total hip arthroplasty (THA) implants[1]. However, registry data reporting significantly higher failure rates and revision rates caused concern[2,3]. Adverse reaction to metal debris (ARMD) released as metal particles, which may result in macroscopic necrosis of the periprosthetic space, corrosive osteolysis; large, sterile hip effusions; and periprosthetic solid and cystic masses (pseudotumors), was thought to contribute to the high failure rates[4]. In addition, histologic findings of surgical specimens exhibited a specific lymphocyte-dominant immunologic response, now known as aseptic lymphocyte-dominant vasculitis-associated lesion (ALVAL)[5].

This case report describes recurrent hip joint effusion and pseudotumor formation after revision THA as a result of MoM-related ALVAL disease. Management of the recurrent pseudotumor with locally infused tigecycline (trade name, Tygecil) as a sclerosing agent is discussed.

CASE PRESENTATION

Chief complaints
A female aged 73 years, with hypertension and right hip osteoarthritis, visited our clinic due to recurrent right hip mass after receiving MoM THA (CONSERVE® total Hip system, BFH with Spiked Shell, Wright Medical, Inc., Arlington, TN) surgery seven years ago (Figure 1A). The patient's signs were soft tissue swelling with mild tenderness, but no local heating, and no erythematous changes of the skin.

History of present illness
She had MoM THA surgery seven years ago, and had recurrent right hip mass.

History of past illness
The patient had hypertension and was under medication control.

Personal and family history
The patient had hypertension and right hip osteoarthritis. There was no significant family medical history to note.

Physical examination
Physical examination revealed soft tissue swelling with mild tenderness, but no local heating, and no erythematous changes of the skin.
Figure 1 Pre-operative and post-operative series images. A: Radiography of metal-on-metal total hip arthroplasty (THA) over right hip; B: The metal-on-metal acetabular cup and femoral head removed from revision surgery. Surface scratching and erosion was observed between the cup/head component; C: Pre-operative gross photo (AP view) of right hip showed mass protruding at lateral side of right hip; D and E: Radiography and gross photo of revision ceramic-on-polyethylene THA; F: Post-revision gross photo (lateral view) of patient after locally tigecycline injection showed subsidence of the mass at 24-mo follow-up.

Laboratory examinations
Laboratory examinations of serum C-reactive protein and erythrocyte sedimentation rate revealed that these were within the normal ranges, excluding the possibility of infection. Analysis of synovial fluid drainage also ruled out the likelihood of infection. Examinations of serum levels of cobalt and chromium revealed that these were within the normal ranges.

Imaging examinations
Magnetic resonance imaging (MRI) images with multiacquisition variable-resonance image combination (MAVRIC) of right hip showed joint effusion and trochanteric bursitis involving the right lateral side of the right artificial hip (Figure 2A).

FINAL DIAGNOSIS
Formation of metallosis-related pseudotumor was suggested. According to the normal serum levels of cobalt and chromium, and the patient’s poor response to conservative treatment (oral nonsteroidal anti-inflammatory drug, antihistamine and local injection of steroid), surgical interventions of right hip arthrotomy and bursectomy was performed. After removing all hypertrophic bursa, necrotic periprosthetic soft tissue and pseudotumor, the synovial lining cell hyperplasia with lymphocytic cells infiltration, stromal fibroplasia, and massive fibrin exudation confirmed the histological diagnosis of ALVAL[6] (Figure 3).

TREATMENT
We performed ceramic-on-polyethylene THA (Biolox delta Option, Biomet G7, Zimmer Biomet, Inc., Warsaw, IN) to treat persistent postoperative effusion and soft tissue swelling following revision (Figure 1D). However, persistent joint effusion (about 100 mL-daily straw fluid from drainage) was still noted for two months after revision THA. Infection was excluded after checking the drainage fluid culture and
Figure 2 Magnetic resonance imaging series of pre-operative, post-revision surgery, and after Tigecycline local treatment. A: Initial radiographic evaluation: magnetic resonance imaging (MRI) image of right hip showed joint effusion and trochanteric bursitis involving right lateral subcutaneous layer of right artificial hip. The finding corresponds to the diagnosis of pseudotumor; B: MRI image following revision total hip arthroplasty (THA): recurrent periprosthetic pseudotumor over right hip to lateral subcutaneous layer and adjacent subcutaneous inflammation; C: MRI image following revision THA, one month after local tigecycline infusion, showed subsidence of recurrent pseudotumor, periprosthetic soft tissue swelling and effusion.

Figure 3 Gross photo and pathological section of resected pseudotumor. A: Photograph of debrided necrotic tissues taken from arthrotomy and removal of pseudotumor; B: Synovial lining cell hyperplasia with lymphocytic cells infiltration and Stromal fibroplasia, with the histological diagnosis of aseptic aseptic lymphocyte-dominant vasculitis-associated lesion.

performing the microscopic tests. Repeat MRI revealed recurrent periprosthetic pseudotumor after revision THA (Figure 2B). Chemical pleurodesis treatment for pleural effusion using tetracycline (single-dose tigecycline 50 mg into the joint space and periprosthetic soft tissue) was performed one week after revision THA.

OUTCOME AND FOLLOW-UP

The effusion was much improved one week after the local tigecycline infusion. Following MRI scan also showed subsidence of pseudotumor, only minimal subcutaneous fibrotic scaring tissue, without effusion collection was noted (Figure 2C). No recurrent effusion or recurrent pseudotumor was found at the end of 24-mo postoperative follow-up (Figure 1F).

DISCUSSION

ALVAL is a histological diagnosis of adverse ARMD in MoM THA, consisting of related metallosis and type IV hypersensitivity reaction[5]. Severe complications were reported, including dislocation, recurrent ALVAL and re-revision requiring post-revision surgery. In this case, before receiving revision THA, chronic periprosthetic soft tissue swelling with pseudotumor formation, complicated by massive effusion, was noted. For lesion evaluation, MRI image with MAVRIC was used in the coronal plane to reduce susceptibility artifact[7]. The pseudotumor recurred even after surgical
interventions of arthroscopy and bursectomy. In response, we arranged revision ceramic-on-polyethylene THA for this case. However, the pseudotumor and soft tissue effusion still recurred after revision THA within post-operative two months. Higher rates of complication, including instability, neurovascular injury, deep infection, reoperation, component loosening had been reported in revision cases for failed MoM hip implants[8]. However, for the present recurrent pseudotumor with persist effusion condition after revision THA with non-MoM component, only few cases were reported and there is no specific management guidelines available[9]. Residual metal debris within soft tissue or persisted hypersensitivity reaction maybe the cause of recurrent pseudotumor. In this case, after excluding infection conditions, local treatment with tigecycline was used as a sclerosing agent. Tigecycline is a broad spectrum antibiotic derivation of tetracycline, which has demonstrated to be an effective sclerosing agent for pleurodesis of different type pleural effusion[10]. The sclerosing agent application to the primary target as pleural mesothelial lining results in the release of several mediators like interleukin-8, transforming growth factor-beta and basic fibroblast growth factor[11]. This leads the diffuse inflammation activity in the cavity, which causes coagulation-fibrinolysis imbalance. This imbalance results in favoring the production of fibrin chain, collagen and extracellular matrix components by fibroblast. These mechanisms eventually result in space obliteration[12]. In the literature review, there was no other study reported application of tigecycline as a sclerosing agent for space obliteration other than pleural space. The reason we chose Tigecycline as sclerosing agent was the safe, accessible, and cost-effective. The sclerosing mechanism also worked in the effusion space between periarticular soft tissue by tigecycline infusion, which resulted in obliteration of recurrent pseudotumor. In the article review of safety profile of tigecycline, the gastrointestinal symptoms are the most common reported adverse effects of tigecycline (nausea 26, vomiting 18 and diarrhea 12%)[13]. Incidence of these adverse effect is reported correlating with escalating doses. In the present case, we only injected single dose of tigecycline 50 mg into the joint space and periprosthetic soft tissue. There is no systemic or local side effect occurred in this case. After locally infusion of tigecycline, the joint effusion diminished significantly within one week. During follow-up, hip MRI images also showed subsidence of pseudotumor, and no recurrent joint effusion at 24-mo after the injection (Figure 2C). There was no complication either gait imbalance in following up.

CONCLUSION

Local infusion treatment using tigecycline is safe, cost effective, and able to provide an additional therapeutic adjunct for the treatment of recurrent pseudotumor after revision non-MoM THA in ALVAL cases.

REFERENCES

DOI: 10.1007/s11999-013-2979-6


Acute myocardial infarction induced by eosinophilic granulomatosis with polyangiitis: A case report

Xuan-Dong Jiang, Shan Guo, Wei-Min Zhang

ORCID number: Xuan-Dong Jiang 0000-0002-6533-8112; Shan Guo 0000-0002-0418-2556; Wei-Min Zhang 0000-0001-8264-5723.

Author contributions: Jiang XD and Guo S reviewed the literature and contributed to manuscript drafting; Zhang WM critically revised the manuscript; all authors 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 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).

Country/Territory of origin: China

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report’s scientific quality classification

Abstract

BACKGROUND

Eosinophilic granulomatosis with polyangiitis (EGPA) is a multisystem disease characterized by allergic rhinitis, asthma, and a significantly high eosinophil count in the peripheral blood. It mainly involves the arterioles and venules. When the coronary arteries are invaded, it can lead to acute myocardial infarction (AMI), acute heart failure, and other manifestations that often lead to death in the absence of timely treatment.

CASE SUMMARY

A 69-year-old man was admitted to the emergency department due to chest pain for more than 1 h. He had a past history of bronchial asthma and chronic obstructive pulmonary disease and was diagnosed with AMI and heart failure. Thrombus aspiration of the left circumflex artery and percutaneous transluminal coronary angioplasty were performed immediately. After surgery, the patient was admitted to the intensive care unit. The patient developed eosinophilia, and medical history taking revealed fatigue of both thighs 1 mo prior. Local skin numbness and manifestations of peripheral nerve involvement were found on the lateral side of the right thigh. Skin biopsy of the lower limbs pathologically confirmed EGPA. The patient was treated with methylprednisolone combined with intravenous immunoglobulin and was discharged after 21 d. On follow-up at 7 d after discharge, heart failure recurred. The condition improved after cardiotonic and diuretic treatment, and the patient was discharged.

CONCLUSION

Asthma, impaired cardiac function, and eosinophilia are indicative of EGPA. Delayed diagnosis often leads to heart involvement and death.

Key Words: Acute myocardial infarction; Eosinophilic granulomatosis with polyangiitis; Churg-Strauss syndrome; Heart failure; Asthma; Case report
Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome, is a multi-system disease of unknown etiology. It is characterized by allergic rhinitis, asthma, and significantly increased eosinophil count in the peripheral blood\[1\]. EGPA is a rare disease, with a prevalence rate of 17.8/1000000 individuals \[2\]. The disease usually occurs between 20 and 40 years of age, and it has no sex predilection. Pathologically, it is characterized by vasculitis that mainly involves the arterioles and venules; furthermore, it can invade medium-sized blood vessels, such as the coronary arteries. The main organs involved are the lungs, heart, kidneys, skin, and peripheral nerves, and its pathogenesis may be related to immune abnormality.

CASE PRESENTATION

Chief complaints
A 69-year-old man was admitted to the emergency department on February 7, 2021 due to “chest pain and discomfort for more than 1 h.”

History of present illness
The patient had chest pain and discomfort for more than 1 h. After entering the emergency room, chest tightness and shortness of breath aggravated, and he developed cough accompanied by pink frothy sputum.

History of past illness
In January 2021, he developed fatigue in both thighs and local numbness on the lateral side of his right thigh; thus, he was treated with acupuncture. Due to “chest tightness and shortness of breath,” he was admitted to another hospital for treatment; his blood test revealed a troponin level of 1.29 ng/mL. No significant coronary lesions were found on coronary angiography. Later, he was hospitalized in the Department of Hematology of our hospital. The patient was diagnosed with bronchial asthma, chronic obstructive pulmonary disease with acute lower respiratory tract infection, coronary atherosclerosis with cardiac function grade III (New York Heart Association grade), and prostate hyperplasia. The patient’s condition was improved, and he was discharged.

Personal and family history
The patient had no bad habits, such as smoking and alcohol drinking, and had no family history of diabetes or hypertension.
**Physical examination**
Temperature: 37.8 °C, pulse: 143 beats per minute (bpm), blood pressure: 93/52 mmHg, coarse respiratory sounds in both lungs, wet rales throughout both lungs, enlarged heart boundary toward the left, regular heart rhythm, and no edema in either lower limb.

**Laboratory examinations**
High-sensitivity C-reactive protein: 56.22 mg/L; blood routine: white blood cell count: 21.29 × 10^9/L; eosinophil count: 12.69 × 10^9/L; hemoglobin: 123 g/L; platelet count: 187 × 10^9/L; creatine kinase: 332 U/L; activity of creatine kinase isoenzyme: 50 U/L; pro-B-type natriuretic peptide: 9,117.0 pg/mL; high-sensitivity troponin: 0.488 ng/mL; creatinine: 123 μmol/L, urine routine: occult blood positive (3 +); antinuclear antibodies were positive (+); anti-Ro52 positive (1 +); immunoglobulin IgE: > 2500 IU/mL; and ferritin: > 2000 ng/mL. Pathological examination of skin biopsy specimens of the lower limbs showed eosinophil infiltration in the peripheral blood vessels, as shown in Figure 1.

**Imaging examinations**
Coronary angiography showed no significant stenosis in the right coronary artery, and the distal blood flow was Grade TIMI3. Further, no significant stenosis was found in the left main coronary artery and proximal and middle segments of the left circumflex artery, while the distal segment was occluded. The distal segment of the second obtuse marginal branch was embolized, the middle segment of the left anterior descending coronary artery was 30% narrowed, and the distal segment was occluded, as shown in Figure 2.

Electrocardiography showed inferior wall myocardial infarction, sinus rhythm, ventricular premature beats, poor progressive increase of the R wave in the anterior septum, low voltage in the limb leads, and ST-T changes, as shown in Figure 3. Echocardiography indicated segmental wall motion abnormality (reduced motion in the left ventricular anterior wall and lateral wall from the basal segment to the apical segment, interventricular septum and inferior posterior wall from the middle segment to the apical segment, and apical segment of each ventricular wall), left heart enlargement, mitral regurgitation (mild to moderate), tricuspid regurgitation (mild), and pulmonary hypertension (mild).

**FINAL DIAGNOSIS**
EGPA, cardiogenic shock from acute ST-segment elevation myocardial infarction (Killip class IV), bronchial asthma, chronic obstructive pulmonary disease, and prostatic hyperplasia.

**TREATMENT**
In the emergency department, endotracheal intubation was performed to allow mechanical ventilation. After consultation with the Chest Pain Center, aspirin 300 mg, ticagrelor 180 mg, and atorvastatin calcium 40 mg were administered orally. Thrombus aspiration from the left circumflex artery and percutaneous transluminal coronary angioplasty were immediately performed. During surgery, blood flow recanalization was performed in the left circumflex artery, although blockage reoccurred. Repeated dilation and aspiration were performed, but failed. Unstable respiration and circulation after surgery prompted intensive care unit admission for monitoring and treatment. Norepinephrine 0.38 µg/kg/min was administered to maintain blood pressure. Wet rales were auscultated in both lungs, the whole body was cold and clammy, the skin temperature of the limbs was low, and multiple red ecchymoses scattered in both lower limbs were noted. Cardiogenic shock was considered, and an intra-aortic balloon pump as supportive treatment was provided. The cardiotonic and diuretic, anticoagulation, platelet aggregation inhibition, and other treatments were continued. Pulse index continuous cardiac output monitoring showed a cardiac index of 2.75 L/min; intrathoracic blood volume index of 1168 L/min/m²; global end diastolic volume index of 935 mL/m²; and extravascular lung water index of 16.9 mL/kg. Reexamination of electrocardiography findings indicated sinus tachycardia (123 bpm); poor, progressive increase of the R wave in the anterior
Figure 1 Pathological examination of skin biopsy specimens of the lower limbs showed eosinophil infiltration in the peripheral blood vessels.

Figure 2 Coronary angiogram demonstrated occluded left circumflex arteries, the middle segment of the left anterior descending coronary artery was 30% narrowed, and the distal segment was occluded.

Figure 3 Electrocardiography showed inferior wall myocardial infarction, sinus rhythm, ventricular premature beats, poor progressive increase of the R wave in the anterior septum, low voltage in the limb leads, and ST-T changes. The N-terminal pro-brain natriuretic peptide level was 23,498.0 pg/mL, and the high-sensitivity troponin T level was 3.05 ng/mL. Reexamination of echocardiography findings showed diffusely decreased left ventricular wall motion, decreased left heart function, enlarged left heart, and 40% ejection fraction. The eosinophil count was significantly decreased on day 2 of treatment with methylprednisolone 80 mg once daily combined with intravenous immunoglobulin (IVIG) 20 g once daily.
OUTCOME AND FOLLOW-UP

Endotracheal extubation was performed after 11 d, and the intra-aortic balloon pump was removed after 15 d. He was transferred to the Department of Cardiology after 20 d and discharged after 21 d. Follow-up at 7 d post-discharge showed recurrent heart failure, and he was readmitted. Color Doppler echocardiography indicated decreased contractile activity of the whole left ventricular wall, enlarged left atrium and left ventricle, moderate pulmonary hypertension with severe tricuspid regurgitation, moderate mitral regurgitation, mild regurgitation of the aortic and pulmonary valves, and pericardial effusion. Chest computed tomography showed signs of acute pulmonary edema with bilateral pleural effusion accompanied by atelectasis in the lower lobes of both lungs, an enlarged heart, and a small amount of pericardial effusion. The use of hormones was continued. The patient’s condition improved after cardiotonic and diuretic treatment, and he was discharged after 10 d.

DISCUSSION

We report a 69-year-old man who was diagnosed with acute myocardial infarction (AMI) and unexplained heart failure. The patient was eventually diagnosed with EGPA. To date, EGPA is still diagnosed according to the criteria published by the American College of Rheumatology in 1990[3]: (1) Asthma: History of wheezing or diffuse high-pitched rales when exhaling; (2) Eosinophilia: Eosinophils in the white blood cell, an absolute number > 1500/µL or percentage > 10%; (3) Single or multiple neuropathy, i.e., stocking-and-glove distribution; (4) Unstable pulmonary infiltration: Migratory or temporary pulmonary infiltration on chest radiographs due to systemic vasculitis; (5) Sinusitis; and (6) Extravascular eosinophil infiltration: pathological examination showing eosinophil infiltration around the arteries, arterioles, and veins. Those who meet at least four of the above items are diagnosed with EGPA. The current patient had AMI, heart failure, cardiogenic shock, skin and peripheral nerve involvement, and a past history of asthma for many years. Combined with extravascular eosinophil infiltration on pathological examination, he satisfied the diagnostic criteria.

The most common cause of myocardial infarction is thrombosis under the background of coronary atherosclerosis, which leads to a decrease in coronary blood flow. Coronary angiography of this patient showed that the walls of the major coronary arteries, such as the right coronary artery and left main coronary artery, were smooth. Further, the distal segments of the left circumflex artery and left anterior descending artery were occluded. During surgery, the left circumflex artery was repeatedly dilated and aspirated. It had blood flow recanalization, although blockage reoccurred. In contrast to common AMI in the coronary vessels, recanalization yielded an unsatisfactory effect. The dynamic observation on electrocardiography and B-ultrasonography later cannot explain severe heart failure and cardiogenic shock; thus, other rare causes of myocardial infarction should be considered.

Such cases are very rare. A similar case[4] reported a young man with ST-elevation myocardial infarction accompanied by severe triple-vessel disease. Complete recovery was achieved after immunosuppressive treatment. In another case report, a 45-year-old woman[5] presented with acute coronary syndrome that recurred after drug treatment, and finally EGPA causing coronary artery inflammation was considered. Heart involvement is one of the serious manifestations of EGPA; it is mainly caused by eosinophils infiltrating into the myocardium and coronary vasculitis. The main manifestations[6,7] are cardiomyopathy, pericarditis, and heart failure. Patients with delayed treatment primarily die of AMI or acute heart failure. Multivariate logistic regression analysis of 121 patients with EGPA in Japan[8] showed that myocardial involvement is a risk factor for EGPA recurrence. Therefore, the heart failure in our patient might have been caused by multiple factors, such as coronary vasospasm, vasculitis, and even myocarditis[9].

High-dose glucocorticoids are currently the first choice for EGPA treatment[10]. Most patients respond well to glucocorticoids, although approximately 20% of them still require immunosuppressants. Some experts suggested that IVIG can be used as a second-line treatment for patients with EGPA taking glucocorticoids (and/or other immunosuppressive agents)[11]. Our patient had severe heart failure, and IVIG was added in addition to the glucocorticoids. The eosinophil count was significantly decreased the next day. A similar study[12] found that large-dose intravenous IVIG treatment can significantly improve cardiac function, and patients respond well to this
treatment strategy. Early and effective treatment provides a relatively good prognosis. The main cause of death in EGPA is refractory heart failure caused by myocardial involvement. Heart failure recurred after discharge in our patient, although this was improved after active treatment. Therefore, for such patients, the use of glucocorticoids is very important post-discharge.

CONCLUSION

EGPA can be easily misdiagnosed, resulting in delayed treatment. Asthma, impaired cardiac function, and eosinophilia are helpful symptoms, and this rare disease can be detected on biopsy. Early diagnosis can improve the prognosis in such patients.

REFERENCES

Aggressive natural killer cell leukemia with skin manifestation associated with hemophagocytic lymphohistiocytosis: A case report

Xiao-Huan Peng, Lian-Sheng Zhang, Li-Juan Li, Xiao-Jia Guo, Yang Liu

Abstract

BACKGROUND
Aggressive natural killer cell leukemia (ANKL) is a rare natural killer cell neoplasm characterized by systemic infiltration of Epstein–Barr virus and rapidly progressive clinical course. ANKL can be accompanied with hemophagocytic lymphohistiocytosis (HLH). Here, we report a case of ANKL with rare skin lesions as an earlier manifestation, accompanied with HLH, and review the literature in terms of etiology, clinical manifestation, diagnosis and treatment.

CASE SUMMARY
A 30-year-old woman from Northwest China presented with the clinical characteristics of jaundice, fever, erythema, splenomegaly, progressive hemocytopenia, liver failure, quantities of abnormal cells in bone marrow, and associated HLH. The immunophenotypes of abnormal cells were positive for CD2, cCD3, CD7, CD56, CD38 and negative for sCD3, CD8 and CD117. The diagnosis of ANKL complicated with HLH was confirmed. Following the initial diagnosis and supplementary treatment, the patient received chemotherapy with VDLP regimen (vincristine, daunorubicin, L-asparaginase and prednisone). However, the patient had severe adverse reactions and complication such as severe hematochezia, neutropenia, and multiple organ dysfunction syndrome, and died a few days later.

CONCLUSION
This is the first reported case of ANKL with rare skin lesions as an earlier manifestation and associated with HLH.

Key Words: Aggressive natural killer cell leukemia; Hemophagocytic lymphohistiocytosis; Rare skin lesions; Epstein–Barr virus; Diagnosis and treatment; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
Aggressive natural killer cell leukemia (ANKL) is a rare natural killer (NK) cell neoplasm characterized by systemic infiltration of Epstein–Barr virus and rapid development. Diagnosis and treatment of ANKL can be challenging due to its rapid development, rare nature, and varied clinical manifestations. Extranodal nasal NK/T cell leukemia, indolent NK cell lymphoproliferative disease, and T-large granular lymphoblastic leukemia must be considered in differential diagnosis. Standard therapy for ANKL has not been established because of its rare nature, rapid development, and poor prognosis. This is the first reported case of ANKL associated with hemophagocytic lymphohistiocytosis and rare skin lesions simultaneously.

Core Tip: Aggressive natural killer cell leukemia (ANKL) is a rare natural killer (NK) cell neoplasm characterized by systemic infiltration of Epstein–Barr virus and rapid development. Diagnosis and treatment of ANKL can be challenging due to its rapid development, rare nature, and varied clinical manifestations. Extranodal nasal NK/T cell leukemia, indolent NK cell lymphoproliferative disease, and T-large granular lymphoblastic leukemia must be considered in differential diagnosis. Standard therapy for ANKL has not been established because of its rare nature, rapid development, and poor prognosis. This is the first reported case of ANKL associated with hemophagocytic lymphohistiocytosis and rare skin lesions simultaneously.

URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10708.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10708

INTRODUCTION
Aggressive natural killer cell leukemia (ANKL) is a rare mature natural killer (NK) cell malignant lymphoproliferative disease associated with Epstein–Barr virus (EBV) infection[1]. In general, patients with ANKL present with systemic symptoms, pancytopenia and hepatosplenomegalicy. The skin lesion as an earlier manifestation of ANKL is very rare. ANKL runs an aggressive course and is usually rapidly fatal, with a median survival of only 2 mo[2]. Only early diagnosis, active control of complications, prevention of further deterioration of the disease, and effective chemotherapy can win time for the survival of patients. We report the case of a 30-year-old that was diagnosed as ANKL associated with hemophagocytic lymphohistiocytosis (HLH).

CASE PRESENTATION

Chief complaints
A 30-year-old female patient presented to our Department of Hematology Medicine complaining of fatigue, abdominal distension for 1 mo, and yellow staining of skin and scattered erythema for 10 d.

History of present illness
She had been treated with antibiotics and Chinese patent drug for 3 d for a cold before admission to our hospital. However, the symptoms were not significantly improved. Abdominal distension became more serious with nausea and vomiting, then yellow staining and dense flaky erythema appeared across the whole body skin, mucous membranes and sclera. She was presented to our hospital.

History of past illness
There was no history of past illness.

Personal and family history
She and her family had no specific disease history. Both parents and one older brother were in good health.

Physical examination
Physical examination revealed that the whole skin, mucous membranes and sclera were yellow stained, and dense flaky erythema with scattered bleeding spots of different sizes were found on the forehead, behind the ears, neck and chest (Figure 1A), and the liver and spleen were obviously enlarged.

Laboratory examinations
The blood cell counts were as follows: hemoglobin (HGB) 97 g/L, platelets (PLTs) 15 ×
Figure 1 Physical examination and positron emission tomography/computed tomography scan (PET/CT). A: The forehead, behind the ears, neck and chest had dense flaky erythema with scattered bleeding spots of different sizes; B: PET/CT showed that metabolism was obviously increased in the right nasal cavity, right maxillary sinus, right frontal sinus, partial ethmoid sinus, bilateral sphenoid sinus, right turbinate, nasopharynx, uterus, tail of pancreas, bilateral breast, multiple lymph nodes, liver and spleen, and bone marrow.

10^9/L and leukocytes 22.92 × 10^9/L. Biochemical tests showed marked increased level of total bilirubin to 250.6 μmol/L, direct bilirubin to 221.6 μmol/L, alanine transaminase to 270 U/L, aspartate transaminase to 341 U/L, lactate dehydrogenase to 8527 U/L, and marked decreased level of the total protein to 53.1 g/L. The laboratory findings also found coagulopathy [high level of D-dimer (1.51 μg/mL) and fibrinogen degradation product (5.70 μg/mL)]. Bone marrow aspiration showed that cells with unknown classification and abnormality were easy to see, accounting for 94% (Figure 2A). Bone marrow biopsy test showed that hematopoietic tissue proliferation was heterogeneous, granulocyte and erythrocytic proliferation were decreased, megakaryocytic hyperplasia (0–4/high-power field) was scattered (Figure 2B). Immunohistochemistry of bone marrow biopsy showed that these atypical cells were positive for cCD3, CD20, CD34, CD68, CD56, CD2, CD7, and negative for sCD3
Hematoxylin–eosin staining. A: Bone marrow cell morphology test showed that cells with unknown classification and abnormality were easy to see, accounting for 94% (magnification: 4 × 10 and 10 × 10); B: Bone marrow biopsy test showed that hematopoietic tissue proliferation was heterogeneous, adipose tissue hyperplasia was decreased, granulocyte and erythrocytic proliferation was decreased, megakaryocytic hyperplasia (0–4/high-power field) was scattered (magnification: 10 × 10 and 10 × 40); C: Immunohistochemical of bone marrow biopsy showed that the atypical cells were positive for CD2, cCD3, CD7, CD20, CD34, CD68, CD56, and negative for sCD3 (magnification: 10 × 10; 10 × 40 and 10 × 10).

Serological tests for EBV revealed that EBV DNA was $7.22 \times 10^6$ copies. Multicolor flow cytometry revealed that abnormal cell populations of 90% were seen in areas where CD45 was strongly positive, expressing HLA-DR, CD2, CD7, CD38 and cCD3, and partially expressing CD56. Abnormal NK cells could be seen in the samples, considering the possible source of NK/T cells. TCR gene rearrangement test was negative.

Imaging examinations
Positron emission tomography (PET)/computed tomography (CT) of the whole body showed that metabolism was increased in multiple parts (Figure 1B). PET/CT revealed that malignant tumor cells of the lymphoid hematopoietic system accumulated in multiple organs.

FINAL DIAGNOSIS
According to the clinical manifestation, laboratory and imaging examination, the patient was diagnosed with ANKL associated with HLH[3].

TREATMENT
Following the initial diagnosis and supplementary treatment of malignant tumors, such as transfusion of gammaglobulin, HGB, plasma and PLTs, the patient underwent chemotherapy with VDLP regimen (vincristine, daunorubicin, L-asparaginase and prednisone).
OUTCOME AND FOLLOW-UP

The patient had severe stomachache and vomiting on the second day of chemotherapy, and symptomatic support treatment such as proton pump inhibitor and antiemetic was given. On the third day of chemotherapy, severe hematochezia occurred. Blood pressure began to decrease; heart rate increased to 180 beats/min, HGB, and leukocyte and PLT counts were extremely low, especially PLTs. Considering ANKL complicated with HLH, neutropenia, myelosuppression, multiple organ dysfunction syndrome (MODS), the patient was transferred to the intensive care unit. The general condition of the patient did not improve and deteriorated. Finally, the patient died a few days later.

DISCUSSION

ANKL is a rare entity with < 200 cases published to date, and is always associated with EBV infection[1]. In 1986, Suzuki et al.[4] put forward the concept of ANKL for the first time. In 2001, the World Health Organization classified it as ANKL in the classification of lymphoid tissue tumors, and extranodal NK/T cell lymphoma and extranodal nasal NK/TX cell leukemia (ENKTCL) were both mature NK cell tumors[5]. With the emergence of the next generation of sequencing technology, the molecular basis of ANKL has been clarified. In recent years, the introduction of combined chemotherapy including L-asparaginase (L-ASP), and allogeneic hematopoietic cell transplantation, has helped some patients achieve complete remission and potential cure in theory[6]. However, the prognosis of ANKL is still poor, with a median survival time of 2 mo[7].

ANKL is a systemic disease; the main clinical symptoms are obvious B symptoms, including high fever, fatigue, night sweats, loss of appetite, weight loss, jaundice, and hepatosplenomegaly[8]. The blood cell counts are mostly one-line or multi-line progressive decrease, and the activity of serum lactate dehydrogenase and FASL levels are often high[9]. ANKL is often associated with HLH. Compared with ENKTCL, skin damage is rare[8]. The course of the disease is outbreak, usually accompanied by diffuse intravascular coagulation, leading to multiple organ failure, which progresses to death within a few weeks.

At present, there are no unified diagnostic criteria for ANKL and the more recognized diagnostic criteria are: (1) More immature large granular leukocytes in peripheral blood and bone marrow; (2) Rapidly progressive B symptoms, liver, spleen and lymph node enlargement, neutropenia, low HGB, thrombocytopenia, liver function and blood coagulation abnormalities; (3) EBV antibody or DNA positive; (4) Immunophenotype conforms to CD2+ CD56+ sCD3 TCRαβ TCRγδ; (5) Common chromosomal abnormalities del; and (6) q21q25[10]. The genetic changes of ANKL are largely unknown, which is in sharp contrast to the rich genetic information of ENKTCL; a disease closely related to ANKL. Some gene mutations in ANKL, including the JAK–STAT and Ras–MAPK systems, are found in the signal transduction system. Some studies have shown that the frequent mutations in the JAK–STAT signaling system are STAT3 or STAT5B. STAT3 represents the most frequently mutated gene (~20% of cases)[11]. Tumor suppressor genes TP53 and DDX3X, epigenetic modification genes CREBBP, TET2, MLL2, BCOR and SETD2 and hypermethylation mutation of HACE1 have also been described in ANKL[12]. However, in terms of clinical practice, the diagnosis of ANKL still depends to a large extent on leukemic cells with abnormal morphology and immunophenotype. Chromosome gain and loss, STAT3 and STAT5B mutations, and HACE1 hypermethylation were detected only in sporadic cases.

HLH is also a rare hematological disease, but it is one of the common complications of ANKL. In one published study, there were 34 patients with ANKL, of which 19 (56%) developed HLH during the course of treatment[13]. It was secondary HLH because it was secondary to NK cell leukemia.

Initially, a large area of dense flaky erythema with scattered bleeding spots of different sizes appeared on the forehead, behind the ears, neck and chest. We found no relevant reports in the literature. It has been reported that skin lesions in ANKL are relatively rare compared with ENKTCL[7], but skin lesions were found in the present case. The patient died due to rapid progression of the disease; therefore, we lost the opportunity to clarify the nature of the skin lesions and their relationship with the primary disease. The systemic invasion of tumor cells in this patient was obvious, so it can be speculated that the condition was complicated with rare skin lesions.
At present, there are no unified clinical treatment standards or prospective clinical trials specifically for ANKL. The widely accepted clinical chemotherapy regimens are: CHOP-like regimen (including anthracycline and vincristine), L-ASP + methotrexate + dexamethasone regimen, SMILE (dexamethasone + methotrexate + ifosfamide + L-ASP + VP16) regimen, and acute lymphoblastic leukemia intensive chemotherapy (VDLP) regimen [10]. Some studies have shown that the high expression of P-glycoprotein encoded by multidrug resistance gene MDR1 in NK tumor cells may be related to the poor response of ANKL to chemotherapy and relapse after chemotherapy [14]. Most studies have shown that antineoplastic drugs whose action mechanism was not affected by P-glycoprotein, such as L-ASP, had an effect on ANKL, especially in high-risk patients [15]. The chemotherapy regimens based on MTX, L-ASP and VP16, such as SMILE, have shown promising results [16]. Allogeneic hematopoietic stem cell transplantation after remission is the main method to improve the prognosis of ANKL patients.

In the present case of ANKL complicated with HLH, disease progression was rapid. According to current research, it was suggested that SMILE or L-ASP + methotrexate + dexamethasone regimen should be used to control the primary disease, but considering the poor condition of the patient, she could not tolerate the adverse reactions of SMILE intensive therapy. Finally, VDLP regimen was used. Unfortunately, the patient had severe abdominal pain with vomiting in the course of chemotherapy, serious hematochezia occurred on the third day of chemotherapy, and blood pressure dropped rapidly. The patient died a few days later.

CONCLUSION

ANKL is still a challenging disease due to its rapid development, rare nature, and variety of clinical manifestations. Therefore, only early diagnosis, active control of complications, prevention of further deterioration of the disease, and effective chemotherapy can win time for the survival of patients.

ACKNOWLEDGMENTS

We are thankful to the family of the patient for permitting us to use their case for presentation.

REFERENCES

1 Lima M. Aggressive mature natural killer cell neoplasms: from epidemiology to diagnosis. Orphanet J Rare Dis 2013; 8: 95 [PMID: 23816348 DOI: 10.1186/1750-1172-8-95]


Chronic lymphocytic leukemia/small lymphocytic lymphoma complicated with skin Langerhans cell sarcoma: A case report

Shao-Yan Li, Yan Wang, Li-Hua Wang

ORCID number: Shao-Yan Li 0000-0001-6897-191X; Yan Wang 0000-0001-9985-4011; Li-Hua Wang 0000-0001-9538-3945.

Author contributions: Li SY and Wang LH carried out the studies, participated in collecting data, and drafted the manuscript; Wang Y performed the statistical analysis and participated in its design; All authors read and approved the final manuscript.

Informed consent statement: Consent was obtained from relatives of 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).

Country/Territory of origin: China

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report’s scientific

Abstract

BACKGROUND
Langerhans cell sarcoma (LCS) is a rare malignancy with poor prognosis. LCS and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) can occur in the same diseased tissues, such as lymph nodes or skin.

CASE SUMMARY
A 48-year-old female Han Chinese patient was admitted for generalized lymph node enlargement for 6 years and abdominal distension for 1 wk. She was diagnosed with small B-cell lymphoma (stage IV)/CLL (Benet stage B) and received chemotherapy. She started oral ibrutinib in February 2019. She was hospitalized on June 11, 2019, and a 1.5 cm × 1.5 cm dark-red nodule with ulceration scalp lesion was found. Biopsy revealed LCS but without CLL/SLL. She was diagnosed with CLL/SLL (Binet stage C, Rai stage IV) accompanied by secondary histiocytic sarcomas and skin LCS and received cyclophosphamide, doxorubicin, vincristine, dexamethasone, and etoposide but developed severe cytopenia. She ultimately refused treatments and discharged spontaneously. She died on September 12, 2019. The literature review showed that in patients with CLL/SLL, skin lesions of LCS are accompanied by lymph nodes or skin.

CONCLUSION
In this patient, the skin lesion of LCS showed no concomitant CLL/SLL.

Key Words: Skin; Langerhans cell sarcomas; Chronic lymphocytic leukemia/small lymphocytic lymphoma; Ibrutinib; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
**CASE PRESENTATION**

**Chief complaints**
A female Han Chinese patient was admitted to the Department of Hematology of Jinan Central Hospital Affiliated to Shandong University. The patient was hospitalized on June 11, 2019 for a fourth time, and a 1.5 cm × 1.5 cm dark-red nodule with ulceration was found on the scalp.

**History of present illness**
The patient was hospitalized on June 11, 2019 for a fourth time, and a 1.5 cm × 1.5 cm dark-red nodule with ulceration was found on the scalp (Figure 1A).

Multiple enlarged subcutaneous masses appeared in the right neck 1 mo after the scalp mass, accompanied by substantial pain and dysphagia. The masses grew rapidly.

**History of past illness**
A 48-year-old female Han Chinese patient was admitted to the Department of Hematology of Jinan Central Hospital Affiliated to Shandong University in May 2012 for generalized lymph node enlargement for 6 years and abdominal distension for 1 wk. On admission, physical examination showed the enlargement of multiple lymph nodes at the bilateral neck, axillary fossa, and inguinal, with varied sizes. The largest lymph node had a 3.0 cm × 4.0 cm size and was hard, without pain upon palpation.

An abdominal mass of 15.0 cm × 10.0 cm was found under the umbilicus, which was round and mobile. A palpable lymph node had a 3.0 cm × 4.0 cm size and was hard, without pain upon palpation. The patient had a lymph node in the right axilla 1.5 cm × 1.5 cm significant, without pain upon palpation.

**Grade classification**
- Grade A (Excellent): A
- Grade B (Very good): 0
- Grade C (Good): 0
- Grade D (Fair): 0
- Grade E (Poor): 0

**Open-Access**: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/license/by-nc/4.0/

**Received**: June 20, 2021
**Peer review started**: June 20, 2021
**First decision**: July 16, 2021
**Revised**: August 14, 2021
**Accepted**: September 16, 2021
**Article in press**: September 16, 2021
**Published online**: December 6, 2021

**P-Reviewer**: Panaitescu C
**S-Editor**: Wang JJ
**L-Editor**: Filipodia
**P-Editor**: Xing YX

**Core Tip**: Langerhans cell sarcoma (LCS) is a rare Langerhans cell malignant tumor with a poor prognosis. Chronic lymphocytic leukemia (CLL) is a hematologic malignancy. We report a patient with a history of CLL/small lymphocytic lymphoma diagnosed with cutaneous LCS by skin biopsy that is different from previously reported cases. In the case report, LCS occurred on the skin, and there was no CLL/small lymphocytic lymphoma in the same lesion. A possible mechanism is that ibrutinib led to the activation of a proto-oncogene that resulted in the malignant transformation of dendritic cells. Still, this hypothesis will have to be explored.

**Citation**: Li SY, Wang Y, Wang LH. Chronic lymphocytic leukemia/small lymphocytic lymphoma complicated with skin Langerhans cell sarcoma: A case report. *World J Clin Cases* 2021; 9(34): 10715-10722
**URL**: https://www.wjgnet.com/2307-8960/full/v9/i34/10715.htm
**DOI**: https://dx.doi.org/10.12998/wjcc.v9.i34.10715

**INTRODUCTION**

Langerhans cell sarcoma (LCS) is a rare Langerhans cell malignant tumor with a poor prognosis[1,2]. LCS displays malignant tumor typical characteristics, such as rapid growth, local invasion, recurrence, and metastasis[2]. Positive immunohistochemical staining for CD1a, CD207 (Langerin), and S-100 protein are confirmatory of LCS[2]. There is a lack of evidence regarding the most appropriate treatment for LCS, but chemotherapy and surgery can be used[2]. Still, the prognosis remains poor, with overall survival of 27 ± 4 mo and disease-free survival of 18 ± 4 mo[2].

Chronic lymphocytic leukemia (CLL) is a hematologic malignancy characterized by progressive accumulation of phenotypically mature malignant B-cell lymphocytes in peripheral blood, bone marrow, and lymph nodes[3]. CLL is the most common leukemia in adults, with a reported incidence of about 4-6 per 100000 people per year in Western countries[3]. Small lymphocytic lymphoma (SLL) is a different manifestation of the same disease as CLL, with the main difference being that abnormal lymphocytes mainly accumulate in lymph nodes and other tissues, with no evidence of cytopenia or bone marrow involvement[3].

LCS and CLL/SLL can occur in the same diseased tissues, such as lymph nodes or skin[4-6]. We report a patient with a history of CLL/SLL diagnosed with cutaneous LCS by skin biopsy, but there was no CLL/SLL in the cutaneous lesion of LCS.
The patient was admitted for the fourth time and was diagnosed as chronic lymphocytic leukemia/small lymphocytic lymphoma complicated with skin Langerhans cell sarcoma. A: Lesion on the left side of the head, looking like a hanging bag, with a soft texture, a slightly hard base, and ulceration and blood scabs at the tip; B: Skin tissue local ulcer formation (hematoxylin and eosin [HE], × 10); C: Ulcer showed mixed cell proliferation, vascular proliferation (HE, × 20); D: Some cells were enlarged, with a rich cytoplasm, light staining, mononuclear, binuclear, multinucleated, or lobulated nucleus; phagocytosis of lymphocytes could be seen in some cytoplasm. In the background, there were more scattered lymphocytes, neutrophils, and local interstitial mucoid degeneration pustular folliculitis (HE, × 100); E: Some cells were enlarged, with a rich cytoplasm, light staining, mononuclear, binuclear, multinucleated, or lobulated nucleus; phagocytosis of lymphocytes could be seen in some cytoplasm. In the background, there were more scattered lymphocytes, neutrophils, and local interstitial mucoid degeneration pustular folliculitis (HE, × 200).

Figure 1 Morphology and skin biopsy of the scalp lesion. The patient was admitted for the fourth time and was diagnosed as chronic lymphocytic leukemia/small lymphocytic lymphoma complicated with skin Langerhans cell sarcoma. A: Lesion on the left side of the head, looking like a hanging bag, with a soft texture, a slightly hard base, and ulceration and blood scabs at the tip; B: Skin tissue local ulcer formation (hematoxylin and eosin [HE], × 10); C: Ulcer showed mixed cell proliferation, vascular proliferation (HE, × 20); D: Some cells were enlarged, with a rich cytoplasm, light staining, mononuclear, binuclear, multinucleated, or lobulated nucleus; phagocytosis of lymphocytes could be seen in some cytoplasm. In the background, there were more scattered lymphocytes, neutrophils, and local interstitial mucoid degeneration pustular folliculitis (HE, × 100); E: Some cells were enlarged, with a rich cytoplasm, light staining, mononuclear, binuclear, multinucleated, or lobulated nucleus; phagocytosis of lymphocytes could be seen in some cytoplasm. In the background, there were more scattered lymphocytes, neutrophils, and local interstitial mucoid degeneration pustular folliculitis (HE, × 200).
Lymphocyte proliferation, which had small cellular bodies and less cytoplasm, round or irregular cellular nuclei, fine and dense chromatin, and unclear nucleoli. Diffused distribution of granulocytes and erythrocytes, which were almost mature, was found. The number of megakaryocytes was not reduced, and they had lobulated nuclei. Reticular fiber staining showed negative results. Immunohistochemistry showed CD20 (+), CD79a (+), CD5 (+), CD23 (+), CD3 (-), and cyclin D1 (-). These findings suggested CLL. Flow cytometry of the bone marrow showed increased monoclonal B lymphocytes (about 68% of the total cells), of which the immune phenotype was CD19 (+), CD20 (-), CD5 (+, some cells), CD10 (-), and CD23 (+, some cells). Restricted expression of the light chain of membrane immunoglobulin K was found, suggesting monoclonal cells. The patient was then diagnosed with small B-cell lymphoma (stage IV)/CLL (Benet stage B). The patient refused rituximab and thus received one cycle of the FC regimen [fludarabine (40 mg, d1; Hanhui Pharmaceutical Co. Ltd, Hangzhou, China) and cyclophosphamide (0.2 g, d1-4; Baxter Oncology Gmbh)]. The superficial lymph nodes and abdominal masses reduced during treatment, and the lymphocyte count reduced from 16.19 × 10^9/L to 1.94 × 10^9/L. She then received two cycles of the FND regimen [fludarabine (50 mg, d1-3), mitoxantrone (10-24 mg; Shandong Luoxin Pharmaceutical Group Co. Ltd, Shenyang, China), and cyclophosphamide (10 mg, d1-5)] on May 31, 2012, and June 23, 2012.

The patient was admitted to the hospital again in May 2013 for rapid enlargement of cervical lymph nodes. The diagnosis on admission was small B-cell lymphoma (stage IV)/CLL (Benet stage B). She received two cycles of FND in May and June 2013. Still, the disease progressed, and she received two cycles of R-FC [rituximab (600 mg, do; Roche Pharma), fludarabine (40 mg, d1-3), and cyclophosphamide (0.3 g, d1-3)] in July and August 2013, followed by one cycle of R-FND [rituximab (600 mg, d0), fludarabine (40 mg, d1-5), mitoxantrone (16 mg, d1), and dexamethasone (20 mg, d1-5)] in September 2013. She received gemcitabine (1.4 g, d1, d8), oxaliplatin (150 mg d1), and dexamethasone (20 mg d1-4, d8-11) in November 2013 due to disease progression.

The patient was hospitalized in February 2018 a third time for evident weakness and generalized lymph node enlargement. The evaluation suggested CLL/SLL stage C and Rai stage IV, which was a high-risk type. High-dose methylprednisolone (0.5 g × 3 d) and gamma globulin (5.0 g × 4 d) was given and followed by R-FC chemotherapy. After six cycles, she was in partial remission. The patient was hospitalized again on February 23, 2019 for generalized lymph node enlargement. The whole abdomen enhanced computed tomography showed multiple enlarged lymph nodes in the neck, chest, and pelvic cavity. Oral ibrutinib (0.42 g, once per day; Catalent CTS LLC) was given, and the lymph nodes diminished in size.

**Personal and family history**

The patient had no history.

**Physical examination**

There was no physical examination.

**Laboratory examinations**

A biopsy showed epidermis absence, ulceration, dermis edema, and diffuse infiltration of tumor cells. Large amounts of large cells and multinucleated giant cell-like tumor cells were found, and pathological nuclear divisions were spotted (Figure 1B-E). Immunohistochemistry showed CD12 (+), S-100 (+), Ki-67 (+, about 30%), CD45 (+), EMA (-), CD15 (-), CK (-), MPO (-), HMB45 (-), CD68 (+, small amount), CD30 (-), CD20 (-), CD3 (-), and CD23 (-) (Figure 2). The pathological diagnosis was a high possibility of interdigitating dendritic cell sarcoma and unclassified dendritic cell tumor (grade 3). Re-examination of the bone marrow showed characteristics of bone marrow changes of CLL/SLL treatment. Flow cytometry of the bone marrow showed that about 5.98% of the cells were abnormally matured lymphocytes, which expressed CD19 and skappa, some cells also expressed CD5, CD23, and CD200, very few cells expressed immunoglobulin M, and no cells expressed CD10, CD20, CD22, CD34, CD79b, FMC-7, or sLambda. Pathological examination of the bone marrow showed generally normal hyperplasia; some sites were with relatively active hyperplasia, and percentages of granulocytes and erythrocytes were normal. The granulocytes and erythrocytes were mainly dominated by cells more naïve than polychromatic or polychromatophilic cells. The number of megakaryocytes was not reduced, and they were mainly with lobulated nuclei. Lymphoid hyperplasia was found, which showed multifocal distribution, and showed reticular fiber staining (2+), CD3 (-), CD5 (+, some cells), CD20 (+), CD23 (+), CD1a (-), Mum-1 (-), CD79a (+), Ki67 (+, 30%), CD30 (-),
CD10 (+, limited cells), S-100 (-), and BCL-6 (-). Findings of the bone marrow examination still met the diagnosis of CLL/SLL.

The scalp mass showed local ulceration of the skin tissues, with mixed cell proliferation and angiogenesis. Some cells were of increased sizes and rich cytoplasm, which were lightly stained and with single nuclear, double nuclei, multiple nuclei, or lobulated nuclei. Lymphocytosis was found in the cytoplasm of some cells, and relatively large amounts of sporadic lymphocytes and neutrophils were found in the background. Mucoid degeneration was found in local interstitial substance, CD1a (+), CD3 (-), CD15 (-), CD20 (-), CD21 (-), CD23 (-), CD30 (+, few), CD45 (+), CD68 (+), S-100 (+, small amount), CK (+, epithelium), EMA (-), Ki67 (+ 80%), MPO (-), and HMB45 (-). In situ hybridization showed Epstein-Barr virus (EBV) -EBVR (-). The patient was diagnosed with skin LCS. A biopsy of the right neck mass showed histiocytic sarcomas. Some areas showed undifferentiated sarcomatoid changes and
CD3 (-), C20 (-), CD68 (+), Ki-67 (+, about 15%), CD21 (-), CK (-), HMB45 (-), S-100 (-), CD1a (-), and LCA (+). The patient was then diagnosed with CLL/SLL (Binet stage C, Rai stage IV) accompanied by secondary histiocytic sarcomas and skin LCS.

**Imaging examinations**

There were no imaging examinations.

**FINAL DIAGNOSIS**

CLL/SLL (Binet stage C, Rai stage IV) accompanied by secondary histiocytic sarcomas and skin LCS.

**TREATMENT**

Ibrutinib (0.42 g, QD) was continued.

As LCS is aggressive, the CHOP-E regimen [cyclophosphamide 1.2 g d1, doxorubicin (Wanle Pharmaceutical Co. Ltd, Shenzhen) 80 mg d1, vincristine (Minsheng Pharmaceutical Co. Ltd, Hangzhou) 4 mg d1, etoposide (Qilu Pharmaceutical Co. Ltd) 75 mg d3-5, and dexamethasone 10 mg d1, 15 mg d2-4, 20 mg d5-7, and 15 mg d8-14] was given. The mass in the right neck decreased, but severe bone marrow suppression occurred. Leucocyte promotion and platelet and red blood cell infusion were performed.

**OUTCOME AND FOLLOW-UP**

The patient died of an acute intracerebral hemorrhage on September 12, 2019.

**DISCUSSION**

Langerhans cells are dendritic cells (DC) located in epithelial tissues and act as antigen-presenting cells[2]. LCS is an extremely rare tumor and has a very poor prognosis. The median age at presentation is 50 years, and the ratio of male to female is 1.3. Most patients die within 2 years after diagnosis. The patient reported here died 3 mo after the diagnosis of LCS[2].

The etiological factors of LCS include immunosuppression, viruses, and previous hematological diseases[2]. Immunosuppression (such as calcineurin inhibitors) can increase the risk of malignant tumors (2.7-13.7-fold), which increases with the intensity and duration of immunosuppression[7]. Cutaneous and lymphoproliferative malignant tumors are among the most common malignant tumors after transplantation[8]. Malignant tumors induced by EBV and human papillomavirus virus are the most common post-transplant cancers[9]. Merkel cell polyomavirus DNA was detected in LCS tissue samples of 7 LCS patients, and the amplification level was higher than that in Merkel cell polyomavirus-positive Langerhans cell histiocytosis; it was speculated that LCS is likely to be the result of viral infection[10]. Still, the case reported here had no history of organ transplantation, no use of calcineurin inhibitors, and negative EBV mRNA. It is unlikely that the above causes induced the LCS.

A primary history of CLL/SLL and long-term use of immunosuppressive agents may be the cause of skin LCS[2,4,6,11-13]. Previous studies showed that some CLL/SLL could transform into aggressive hematopoietic tumors of another lineage, such as LCS[2,4,6,11-13]. LCS clonally related to low-grade B-cell lymphomas and leukemias has been described[4-6]. Among the previous studies, one reported that the two malignancies were detected in the same skin biopsy[4], and three other studies reported that the two malignancies were detected in the same lymph nodes[5,6,12]. The mechanism is probably the transdifferentiation of the B cell lineage through direct transdifferentiation of neoplastic B cells into malignant histiocytes/DC, tumor lymphocytes dedifferentiate into early progenitor cells, and then progenitor cells redifferentiate into histiocytes/DCs[4]. It has been reported that the BRAF V600E mutation was found in patients with LCS and concurrent CLL/SLL[5,6]. Because CLL/SLL and LCS existed independently in this case, we did not detect a mutation in
the BRAF V600E gene. Besides, the pathogenesis of LCS in this case was unknown.

The Bruton tyrosine kinase (BTK) inhibitor ibrutinib is an inhibitor of the B cell receptor signaling pathway through BTK. It ultimately prevents B cell proliferation, chemotaxis, transport, and adhesion by covalently binding to the cysteine residue (C481) in the ATP binding pocket of BTK. The effective regulation of signal transduction might control the intrinsically invasive tumors to some extent. Still, under the selection pressure by inhibitors targeting the B cell receptor signaling pathway, dedifferentiated or transdifferentiated tumor clones can appear[4,14]. In addition, enhanced maturation of BTK-deficient DC can be stimulated by lipopolysaccharides and their ability to stimulate T cells[15]. After the fusion of mature DC and tumor cells, DC can express tumor antigens in an immunogenic manner. When the DC of the tumor-bearing host engulfs apoptotic or necrotic tumor cells, these DC express tumor antigens in a tolerant manner. The tumor will defeat the host because of the tolerance, produce ubiquitous proto-oncogenes, and transform into malignant clones [16]. Since the case reported here received ibrutinib and ibrutinib can promote the transdifferentiation of B cells into DCs or stimulate the abnormal maturation of DCs, ibrutinib is a possible reason for the development of LCS in the present case. Still, the LCS lesion was not physically found at the same location as a CLL/SLL lesion but might have arisen elsewhere and moved through hematogenous migration. Since not all lesions seen at imaging were biopsied, this remains a possibility.

CONCLUSION

In conclusion, the LCS case reported here is different from the previously reported cases of LCS with CLL/SLL. In the case reported here, LCS occurred on the skin, and there was no CLL/SLL in the same lesion. A possible mechanism is ibrutinib led to the activation of a proto-oncogene, resulting in the malignant transformation of DCs, but this is only a hypothesis.

REFERENCES


Severe mediastinitis and pericarditis after endobronchial ultrasound-guided transbronchial needle aspiration: A case report

Jeong Suk Koh, Yoon Joo Kim, Da Hyun Kang, Jeong Eun Lee, Song-I Lee

CASE REPORT

Severe mediastinitis and pericarditis after endobronchial ultrasound-guided transbronchial needle aspiration: A case report

Jeong Suk Koh, Yoon Joo Kim, Da Hyun Kang, Jeong Eun Lee, Song-I Lee, Department of Pulmonary and Critical Care Medicine, Chungnam National University Hospital, Daejeon 35015, South Korea

Corresponding author: Song-I Lee, MD, Adjunct Professor, Department of Pulmonary and Critical Care Medicine, Chungnam National University Hospital, 282 Munhwa-ro, Jung-gu, Daejeon 35015, South Korea. newcomet01@naver.com

Abstract

BACKGROUND
Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a safe and minimally invasive diagnostic tool for mediastinal and hilum evaluation. However, infectious complications may occur after EBUS-TBNA. Among these, mediastinitis and pericarditis are rare.

CASE SUMMARY
A 67-year-old woman was referred to our hospital due to paratracheal lymph node enlargement on chest computed tomography (CT). EBUS-TBNA was performed on the lymph node lesions, and prophylactic oral antibiotics were administered. Seven days after EBUS-TBNA, the patient visited the emergency room with a high fever and chest pain. Laboratory test results revealed leukocytosis with a left shift and elevated C-reactive protein level (25.7 mg/dL). Chest CT revealed the formation of a mediastinal abscess in the right paratracheal lymph node and pericardial and bilateral pleural effusions. The patient received intravenous antibiotic treatment, cardiac drainage through pericardiocentesis, and surgical management. The patient recovered favorably and was discharged 31 d after the operation.

CONCLUSION
Mediastinitis and pericarditis after EBUS-TBNA are rare but should be considered even after the use of prophylactic antibiotics.

Key Words: Endoscopic ultrasound-guided fine needle aspiration; complication; mediastinitis; pericarditis; antibiotics; case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
Core Tip: Acute mediastinitis and pericarditis are rare complications of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). This case presented with acute mediastinitis and pericarditis that developed despite prophylactic antibiotic use after EBUS-TBNA and improved after antibiotic and surgical management.

INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is used to biopsy enlarged lymph nodes in the mediastinum and hilum to stage patients with lung cancer and to provide a definitive diagnosis of lymph adenopathy. Although EBUS-TBNA is a safer and less invasive procedure than mediastinoscopy, severe complications can occur; A major complication rate of 0.3% was found in one meta-analysis[1]. Complications such as massive bleeding, cardiac tamponade, hemomedastinum, pneumomediastinum and pneumothorax have been reported as a complication of TBNA[1,2]. However, mediastinitis and pericarditis rarely occur after EBUS-TBNA. Here, we report the successful use of cardiac drainage and exploratory thoracotomy for drainage of a mediastinal abscess in a patient who developed acute severe mediastinitis with pericarditis after EBUS-TBNA.

CASE PRESENTATION

Chief complaints

The patient presented with a high fever and chest pain. Seven days after EBUS-TBNA, she visited the emergency room.

History of present illness

A 67-year-old woman was referred to our hospital because of lymph node enlargement on chest computed tomography (CT) (Figure 1). EBUS-TBNA of the right paratracheal lymph node was performed using a 22-gauge needle to obtain the tissue core. A total of 11 punctures were performed due to insufficient tissue cores. Prophylactic antibiotics (amoxicillin/clavulanate) were administered to prevent infectious complications after the procedure. Histological examination of the specimen revealed negative malignant cells and no bacteria.

History of past illness

The patient had no comorbidities.

Personal and family history

The patient and families were previously healthy.

Physical examination

On physical examination, the patient appeared acutely ill with a clear mental status. The patient was febrile (37.8°C) and had a stable blood pressure of 100/68 mmHg, pulse rate of 107 bpm, respiratory rate of 18/min, and body temperature of 37.8°C. The breath sounds on the left side of the chest were decreased.

Laboratory examinations

Laboratory tests revealed leukocytosis with a left shift and the following results: White blood cell count: 14410/mm³; neutrophils: 81.3%; hemoglobin: 9.8 g/dL; platelet count: 198000/mm³. Blood chemistry showed elevated total bilirubin (1.40 mg/dL), aspartate
aminotransferase (132 U/L), and alanine aminotransferase (137 U/L) levels in a normal renal panel. The cardiac enzyme level was normal, and the NT-proBNP level was slightly high (562.6 pg/mL). C-reactive protein level was elevated (25.7 mg/dL) and lactic acid level was within the normal range.

**Imaging examinations**

Chest radiography revealed left lung field haziness with pleural effusion and cardiomegaly (Figure 2). Emergency echocardiography revealed pericardial effusion of > 1 cm, and the blood pressure dropped (85/51 mmHg) after emergency echocardiography; cardiac drainage through the pericardiocentesis was performed. Chest CT showed a mediastinal abscess formation in the right paratracheal lymph node and pericardial and bilateral pleural effusions (Figure 2).

**FINAL DIAGNOSIS**

The final diagnosis in the present case was mediastinitis and pericarditis after EBUS-TBNA.

**TREATMENT**

Intravenous antibiotic treatment was initiated. Exploratory thoracotomy was performed by consulting the thoracic and cardiovascular surgery department. Surgical observation revealed whole lung adhesions, mediastinal abscesses, and effusions in the lymph node area. Surgery was completed after adhesiolysis, irrigation, and drainage.

Postoperatively, laboratory findings and the patient’s general condition gradually improved. The cardiac drainage tube and chest drainage were removed 4 d and 16 d postoperatively, respectively (Figure 3). No bacterial pathogens were detected in the specimens obtained from the pericardial and abscess drainage.

**OUTCOME AND FOLLOW-UP**

The patient recovered favorably and was discharged 31 d after the operation. There was no evidence of recurrence within the 12 mo follow-up period.

**DISCUSSION**

Convex-probe EBUS-TBNA is a minimally invasive diagnostic technique for peritracheal and peribronchial areas[3]. EBUS-TBNA identifies the puncture site through real-time ultrasound guidance, allowing accurate sampling from lesions and cytological and histological diagnosis. The cumulative sensitivity of EUBS-TBNA is
Figure 2 Chest X-ray radiograph and computed tomography. A: Chest X-ray radiograph showed both pleural effusion and cardiomegaly; B and C: Chest computed tomography performed 7 d after ultrasound-guided transbronchial needle aspiration demonstrated (B) an increased size and mediastinal abscess formation in the right paratracheal area and (C) newly developed moderate amounts of pericardial effusion with diffuse pericardial thickening.

Figure 3 Chest X-ray radiograph and computed tomography. A: Chest X-ray radiograph findings improved after removal of the chest tube and drainage catheter; B and C: Chest computed tomography demonstrated (B) a decrease in size of the right paratracheal lymph node and (C) decreased amount of pericardial effusion and improvement in diffuse pericardial thickening.

88%-93% and the cumulative specificity is 100% in lymph node staging of lung cancer [4,5]. The overall major complication rate of this procedure was found to be 0.23%-1.23% in a previous meta-analysis[1,2]. Pneumothorax, hemopericardium, and infections such as mediastinitis, pericarditis, and abscesses are reportedly caused by EBUS-TBNA[1,2]. In 7345 EBUS-TBNA cases in Japan, hemorrhage was the most frequent complication (0.68%), followed by infection (0.19%, mediastinitis, n = 7; pneumonia, n = 4; pericarditis, n = 1; cyst infection, n = 1) and pneumothorax (0.03%)[2]. As such, the probability of mediastinitis and pericarditis occurring as a complication of EBUS-TBNA is very low. In addition, case reports revealing the occurrence of mediastinitis or pericarditis after EBUS-TBNA are rare[6-12]. Antibiotic prophylaxis is not used in most EBUS-TBNA cases. However, in this case, mediastinitis and pericarditis occurred even with the use of prophylactic antibiotics. Antibacterial precautions are not recommended for routine diagnostic bronchoscopy, unless there is a previous history of spleen removal, artificial heart valves, or endocarditis[13]. This patient with an enlarged, homogeneous right paratracheal lymph node underwent diagnostic EBUS-TBNA with a 22-gauge needle to obtain the tissue core. A total of 11 punctures were performed because of insufficient tissue cores. Multiple needle passes would have caused mediastinitis and pericarditis in this patient. There are no definitive guidelines regarding which prophylactic antibiotics should be used and for which patients. Despite the use of amoxicillin/clavulanate in this patient, infectious complications occurred; therefore, further research is needed to determine the optimal antibiotic course.

In this case, the patient recovered with the help of antibiotics, pericardial drainage, and surgery. Mediastinitis, with a mortality rate of approximately 50%, is a life-threatening condition that requires aggressive treatment with both broad-spectrum antibiotics and surgical intervention[14]. Appropriate antibiotic therapy and
pericardial drainage may be helpful in treating infectious pericarditis. If vital signs are unstable, immediate pericardial drainage can help prevent pericardial tamponade in patients[15].

CONCLUSION

In conclusion, we reported a patient who developed mediastinitis and pericarditis as complications of EBUS-TBNA, even after the use of prophylactic antibiotics. Although EBUS-TBNA is a minimally invasive diagnostic and treatment option, the possibility of serious complications needs to be considered. Further research is needed to determine which type of prophylactic antibiotic should be used in at-risk patients.

REFERENCES

Obturator hernia - a rare etiology of lateral thigh pain: A case report

Jun Young Kim, Min Cheol Chang

Abstract

BACKGROUND
Lateral thigh pain is a common complaint in patients visiting a pain clinic. Herein, we describe the case of a patient with lateral thigh pain caused by an obturator hernia.

CASE SUMMARY
An 83-year-old woman visited the emergency room with suddenly aggravated right lateral thigh pain. Magnetic resonance imaging of the thigh revealed no abnormal findings in the lateral thigh area. However, an obturator hernia between the pectineus and obturator externus muscles was observed by chance. Retroperitoneal computed tomography revealed a herniated small bowel with an incarceration point at the right obturator canal and a dilated loop of the small bowel upstream. Ultrasonography of the right inguinal region revealed a distended bowel loop in the right pectineus muscle.

CONCLUSION
Our report provides clinicians with information that an obturator hernia can cause lateral thigh pain.

Key Words: Obturator hernia; Pain; Magnetic resonance image; Computed tomography; Ultrasonography; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: The causes of thigh pain are diverse. Although it is a rare disorder, an obturator hernia should be suspected, and imaging studies should be performed when musculoskeletal disorders causing thigh pain are not found in patients with medial, anterior, or lateral thigh pain. Additionally, our report provides clinicians with information that an obturator hernia can cause lateral thigh pain.
Unsolicited article; Externally peer reviewed.

Peer-review report's scientific quality classification
Grade A (Excellent): 0 
Grade B (Very good): 0 
Grade C (Good): 0 
Grade D (Fair): D 
Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/licenses/by-nc/4.0/

Received: July 27, 2021  
Peer-review started: July 27, 2021  
First decision: September 1, 2021  
Revised: September 2, 2021  
Accepted: October 18, 2021  
Article in press: October 18, 2021  
Published online: December 6, 2021

P-Reviewer: Yoshizawa T  
S-Editor: Yan JP  
L-Editor: A  
P-Editor: Yan JP

Citation: Kim JY, Chang MC. Obturator hernia - a rare etiology of lateral thigh pain: A case report. World J Clin Cases 2021; 9(34): 10728-10732
URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10728.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10728

INTRODUCTION
In pain practice, lateral thigh pain is a common complaint of patients. It is caused by several pathologies, such as radiculopathy due to a herniated lumbar disc or spinal stenosis, femoral cutaneous neuropathy, myofascial pain syndrome, and sprain or strain[1]. Because therapeutic methods differ according to the etiology, accurate diagnosis is important.

Currently, there is insufficient knowledge on pain caused by an obturator hernia. In this regard, we present the case of a patient with lateral thigh pain caused by an obturator hernia and describe the findings of imaging studies.

CASE PRESENTATION

Chief complaints
An 83-year-old woman (height: 147 cm; weight: 42 kg) visited our emergency room owing to suddenly aggravated right lateral thigh pain. The pain intensity assessed using the numeric rating scale (NRS) was 9.

History of present illness
This right lateral thigh pain had persisted for several years and had suddenly worsened on the day of the visit to the emergency room. It was aggravated while standing and walking and was relieved upon sitting or lying. She did not have nausea, vomiting, or abdominal pain.

History of past illness
The patient had no specific history of past illnesses.

Personal and family histories
The patient had no specific personal or family history of illnesses.

Physical examination
Physical examination revealed no tenderness of the right lateral thigh and no motor or sensory deficits. Furthermore, the patient did not exhibit any signs of obturator nerve irritation, such as sensory deficit or pain in the medial thigh area. Deep tendon reflexes in relation to the bilateral knees and ankles were normoactive. The straight leg raise test yielded normal findings for both legs. The patient did not have a specific medical history but had mild chronic back pain (NRS score, 1), which had persisted for > 10 years.

Imaging examinations
Magnetic resonance imaging (MRI) of the right thigh revealed no abnormal findings in the lateral thigh. The right lateral femoral cutaneous nerve was intact. However, an obturator hernia between the pectineus and obturator externus muscles was observed by chance (Figure 1). Retroperitoneal computed tomography (CT) revealed a herniated small bowel with an incarceration point at the right obturator canal and a dilated loop of the small bowel upstream (Figure 1). Ultrasonography (USG) of the right inguinal region revealed a distended bowel loop in the right pectineus muscle (Figure 1).

Because the patient had chronic lower back pain, we suspected that her lateral thigh pain might have been caused by lumbar radicular pain due to spinal disorders. Therefore, we conducted imaging studies of the lumbar spine. Lumbar radiography revealed multilevel degenerative lumbar spondylosis. Moreover, central stenosis at L4-5 was observed on lumbar spine CT. Because the patient’s pain was aggravated while standing and walking, we suspected that her pain was caused by right L5 radiculopathy due to lumbar stenosis at L4-5. We performed selective nerve root injection on the right L5 with dexamethasone 40 mg (1 mL), 2% lidocaine (0.3 mL), and normal
Figure 1 Imaging study of an 83-year-old woman with right lateral thigh pain. A: Axial T2-weighted thigh magnetic resonance (MR) image shows the small bowel (open arrow) located between the right pectineus muscle (orange arrow) and obturator interternus muscle (green arrow); B: Coronal T2-weighted thigh MR image shows the small bowel (open arrow) herniating through the right obturator canal; C and D: Axial (C) and (D) coronal contrast-enhanced retroperitoneal computed tomography (CT) images show the right obturator hernia (open arrow) and strangulation point (yellow arrow) at the right obturator canal; E and F: Axial (E) and (F) coronal contrast-enhanced retroperitoneal CT images show a dilated loop of the small bowel upstream (arrowheads); G and H: Ultrasonographic images of the right inguinal region (G and H) shows a herniated bowel loop (open arrow) below the pectineus muscle (arrowheads) (arrow in G, femoral vessels. saline (0.7 mL). However, no pain was provoked during the injection. Additionally, at 30 min after the selective nerve root injection, no pain relief was achieved. Further, at the 1-week follow-up, no pain reduction was observed.
**FINAL DIAGNOSIS**

The patient was diagnosed with lateral thigh pain caused by a right obturator hernia.

**TREATMENT**

She underwent surgical reduction of the obturator hernia with subsequent mesh repair of the defect.

**OUTCOME AND FOLLOW-UP**

At the 1-wk follow-up after the surgery, her lateral thigh pain had completely subsided. The study was approved by the Institutional Review Board of Yeungnam University Hospital.

**DISCUSSION**

An obturator hernia is a protrusion of both intraperitoneal and extraperitoneal contents through the obturator canal, adjacent to the obturator vessels and nerves\[^2\]. It is a rare disorder, accounting for approximately 0.7% of all hernias\[^3\]. This type of hernia is neither palpable nor externally visible, and its representative symptoms are not specific. Therefore, it often goes unsuspected, undiagnosed, or misdiagnosed\[^4\]. It has been reported that only 20%-30% of obturator hernia cases are correctly diagnosed before surgery\[^5\]. The diagnosis of an obturator hernia is very important because focal strangulation or entrapment of the bowel (lower portion of the ileum) in the hernial orifice can progress to gangrene\[^4\]. Because an obturator hernia is unlikely to be reducible, it is typically treated via open or laparoscopic hernia repair.

The most common symptoms of an obturator hernia are pain and paresthesia along the anterior or medial aspect of the thigh, possibly extending down to the knee\[^2\]. However, these symptoms are not always present. Sometimes, thigh pain may not occur. Furthermore, in a previous study, the pain due to obturator hernia occurred in the lateral thigh area, similar to that in our patient\[^6\]. We suspect that our patient’s lateral thigh pain was a referred pain, that is, pain perceived in an area other than the site of the noxious stimulus. The human brain cannot clearly discriminate the site of an irritated or diseased visceral organ and frequently perceives the associated pain as originating from a remote musculoskeletal area\[^7\].

The diagnosis of an obturator hernia is based on high suspicion and imaging study findings\[^8\]. On CT or MRI, a herniating bowel loop with a defect in the inguinal region is observed\[^4\]. Obturator hernias are typically observed in emaciated and multiparous elderly women\[^9\]. Therefore, when thin elderly women present with unexplained thigh pain (anterior, medial, or lateral areas), CT or MRI scans for evaluating obturator hernias are recommended.

USG of the inguinal area is a useful tool that can be rapidly and easily applied at the bedside of patients who are suspected to have an obturator hernia. Moreover, USG is useful for diagnosing other musculoskeletal disorders, such as muscle tears, nerve entrapment, or bursitis, which can cause thigh pain\[^10,11\].

**CONCLUSION**

In conclusion, the causes of thigh pain are diverse. Although it is a rare disorder, an obturator hernia should be suspected, and the appropriate imaging studies should be performed when musculoskeletal disorders causing thigh pain are not found in patients with medial, anterior, or lateral thigh pain. Furthermore, our report provides clinicians with information that an obturator hernia can cause lateral thigh pain.

**REFERENCES**

1. DeFroda SF, Daniels AH, Deren ME. Differentiating Radiculopathy from Lower Extremity


Tracheal tube misplacement in the thoracic cavity: A case report

Ke-Xin Li, Yu-Ting Luo, Leng Zhou, Jia-Peng Huang, Peng Liang

BACKGROUND
Penetrating neck injuries require prompt recognition, diagnosis and management of critical airways. This case demonstrates an emergent situation that a “medical negligence” was avoided with the aid of end-tidal carbon dioxide (ETCO2) waveform.

CASE SUMMARY
We report a case of malposition of the endotracheal tube into the right hemithoracic cavity for cervical knife trauma, resulting in pneumothorax. Tube placement was not confirmed during emergency airway management, and the patient was directly transferred to the emergency operation room. Assisted by ETCO2 and imaging examinations, the anesthetist timely noticed the absence of ETCO2 waveform and resolved this urgent situation before anesthesia induction.

CONCLUSION
This case emphasizes the necessity of ETCO2 waveform and/or X-ray confirmation of endotracheal intubation even in emergent situations.

Key Words: Penetrating neck injury; Tracheal injury; Endotracheal intubation; Malposition; Pneumothorax; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
hemithoracic cavity for cervical knife trauma, resulting in pneumothorax. Fortunately, the anesthetist timely noticed the absence of end-tidal carbon dioxide (ETCO₂) waveform and reviewed the thoracic computed tomography scanning just before anesthesia induction. This case highlights the role of ETCO₂ waveform and/or chest radiography in confirmation of emergency endotracheal intubation, especially for junior doctors and emergency physicians.

CASE PRESENTATION

Chief complaints
A 28-year-old female patient was admitted to the emergency department with knife injury to the neck for 12 h.

History of present illness
The patient was found to have tracheal injury 1 cm below the thyroid cartilage with severe pain, active bleeding (the specific amount of blood loss was unknown) dyspnea, chest distress, shortness of breath and dysphonia. She was managed with compression packing at a local hospital and was transferred to our hospital for further management.

History of past illness
The patient had a disease-free personal and family history.

Personal and family history
The patient had not the special personal or family history.

Physical examination
On admission, the patient was awake with stable vital signs: temperature 36.6 °C, pulse rate 98 bpm, respiratory rate 22/min and blood pressure 118/70 mmHg. Tissue deficits were identified on the left sternocleidomastoid muscles. Breath sounds were slightly diminished, and dry and moist rales were noticed on both upper lobes.

Laboratory examinations
Leucocyte count was 12.79 × 10⁹/L, where neutrophils accounted for 86.8%. And other examinations were all normal, such as hematocrit and hemoglobin count. Urine analysis was also normal. Prothrombin, partial thromboplastin times, and d-dimers were within normal ranges. Electrocardiogram showed a sinus rhythm.
Imaging examinations
After the endotracheal tube was inserted, the patient underwent urgent imaging examinations for operation preparation. Computed tomographic angiography (CTA) showed that there was no leakage, occlusion or expansion of cervical blood vessels and branches. Emergent cervical computed tomography (CT) scan revealed extensive gas accumulation in the mediastinum and underneath the cervical tissue, and continuous interruption in the anterior part of trachea. Chest CT scan demonstrated that the right hemithoracic cavity with limited pleural effusion was collapsed by 70% approximately. The patchy lesions and shadows suggested slight infection in the right hemithorax.

FINAL DIAGNOSIS
The patient was diagnosed with cervical knife trauma and tracheal injuries, which should be managed by emergency operation.

TREATMENT
The emergency medicine physician inserted a 6.5# endotracheal tube into the wound, and inflated the cuff to prevent bleeding from the lumen into the ruptured trachea. Right chest tube was placed for preventing suspected pneumothorax. The patient was immediately transferred to the operating room for exploration after CT scan was performed, but without final reading and confirmation.

OUTCOME AND FOLLOW-UP
The anesthetist was informed that the airway was secured without aspiration risks. However, the patient was agitated and in respiratory distress with 85% pulse oxygenation on room air. After the tracheal tube was connected with anesthesia circuit, the breathing bag of the anesthesia machine was expanding and shrinking during patient’s spontaneous breathing (25/min). However, ETCO₂ waveform was absent. CT scan was reviewed immediately and revealed that the endotracheal tube entered into the right hemithoracic cavity and the right lung was collapsed by 70% approximately due to extensive pneumothorax (Figure 1).

The anesthesiologist and otolaryngologist immediately reinserted the tracheal tube, connecting it to the ETCO₂ monitor. The tube placement was confirmed carefully before final fixation. Next, the patient underwent open neck exploration, tracheal end-to-end anastomosis, recurrent laryngeal nerve reconstruction and tracheotomy thereafter. The subsequent clinical course was uneventful, the patient was transferred into intensive care unit and discharged after two-week hospitalization.

DISCUSSION
We presented a case of tracheal tube misplacement into the thoracic cavity for neck injury. Although the emergency medicine physicians promptly evaluated and attempted to manage the airway with an awake endotracheal intubation, the tube was inserted into the thoracic cavity and produced pneumothorax. Because the patient was on spontaneous breathing and a chest tube was placed on the same side, breath sounds were heard bilaterally. The patient was sent immediately to the operating room assuming successful airway establishment. Successful airway management should have been confirmed with clinical evaluation, chest radiography, and ETCO₂ detection[4].

Iatrogenic tracheobronchial injuries by intubation have been reported[6-8], including tracheal laceration[9,10] and subcutaneous emphysema[11-13]. Incorrect tube sizes and reintubation may contribute to iatrogenic injuries with direct laryngoscopy after endotracheal intubation[14]. Therefore, some studies recommended awake intubation, flexible fiberoptic bronchoscopy, or direct ultrasound visualization to avoid false passage and tracheal injury[15-18]. When dealing with tracheal trauma from PNI, confirmation of the endotracheal tube placement by ETCO₂ waveform
and/or X-ray/CT scan is mandatory.

CONCLUSION

Airway establishment is the priority option for tracheal injuries, which was an extremely urgent situation for PNI. Emergent evaluation and treatment are challenging. Negligence is inevitable, especially in emergency situations. This case highlights the role of ETCO2 waveform and/or chest radiography in confirmation of emergent endotracheal intubation after emergent intubation, especially for junior doctors and emergent physicians.

REFERENCES

3 Triggiani E, Belsay R. Oesophageal trauma: incidence, diagnosis, and management. Thorax 1977; 32: 241-249 [PMID: 882938 DOI: 10.1136/thx.32.3.241]


Peri-implant keratinized gingiva augmentation using xenogeneic collagen matrix and platelet-rich fibrin: A case report

Chun-Yu Han, De-Zhou Wang, Jian-Fei Bai, Lan-Lan Zhao, Wen-Zhi Song

ORCID number: Chun-Yu Han 0000-0002-7691-9481; De-Zhou Wang 0000-0001-8069-5452; Jian-Fei Bai 0000-0002-0412-7573; Lan-Lan Zhao 0000-0002-2172-7909; Wen-Zhi Song 0000-0001-9019-6614.

Author contributions: Zhao LL and Wang DZ contributed to collecting clinical details; Han CY and Bai JF contributed to drafting and writing the manuscript; Song WZ made substantial contribution to manuscript revision; all authors reviewed and approved the final manuscript.

Informed consent statement: Written 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).

Supported by: Industrial Technology Research and Development Project of Jilin Development and Reform Commission, No. 2021C042-2.

Chun-Yu Han, De-Zhou Wang, Jian-Fei Bai, Lan-Lan Zhao, Wen-Zhi Song, Department of Stomatology, China-Japan Union Hospital, Jilin University, Changchun 130031, Jilin Province, China

Corresponding author: Wen-Zhi Song, PhD, Doctor, Department of Stomatology, China-Japan Union Hospital, Jilin University, No. 126 Xiantai Street, Jingkai District, Changchun 130031, Jilin Province, China. songwz@jlu.edu.cn

Abstract

BACKGROUND
Keratinized gingival insufficiency is a disease attributed to long-term tooth loss, can severely jeopardizes the long-term health of implants. A simple and effective augmentation surgery method should be urgently developed.

CASE SUMMARY
A healthy female patient, 45-year-old, requested implant restoration of her left mandibular first molar and second molar. Before considering a stage II, as suggested from the probing depth measurements, the widths of the mesial, medial, and distal buccal keratinized gingiva of second molar (tooth #37) were measured and found to be 0.5 mm, 0.5 mm, and 0 mm, respectively. This suggested that the gingiva was insufficient to resist damage from bacterial and mechanical stimulation. Accordingly, modified apically repositioned flap (ARF) surgery combined with xenogeneic collagen matrix (XCM) and platelet-rich fibrin (PRF) was employed to increase the width of gingival tissue. After 1 mo of healing, the widths of mesial, medial, and distal buccal keratinized gingiva reached 4 mm, 4 mm, and 3 mm, respectively, and the thickness of the augmented mucosa was 4.5 mm. Subsequently, through the second-stage operation, the patient obtained an ideal soft tissue shape around the implant.

CONCLUSION
For cases with keratinized gingiva widths around implants less than 2mm—the soft tissue width and thickness could be increased by modified ARF surgery combined with XCM and PRF. Moreover, this surgery significantly alleviated patients' pain and ameliorated oral functional comfort.

Key Words: Keratinized gingiva augmentation; Xenogeneic collagen matrix; Platelet-rich fibrin; Case report
A 43-year-old female patient requested implant restoration of the left mandibular first molar and second molar (teeth #36 and #37).

History of present illness
The two implants of teeth #36 and #37 underwent osseointegration for three months. Before stage II surgery, the widths of the mesial, medial, and distal buccal keratinized gingiva of the second molar (tooth #37) were 0.5 mm, 0.5 mm, and 0 mm, respectively (Figure 1B and C), as revealed by clinical observation.

History of past illness
During the medical history review, the patient denied having systematic diseases and a history of smoking.
Figure 1 Three months after implant surgery. A: The cone-beam computer tomography showed that good osseointegration had formed between the implant and bone; B and C: Clinical examination and periodontal probe measurement showed that the width of the buccal keratinized gingiva of tooth #37 was 0.5 mm, 0.5 mm, 0 mm from mesial to distal, respectively.

Personal and family history
The patient denied having personal and family history.

Physical examination
Before stage II surgery, the widths of the mesial, medial, and distal buccal keratinized gingiva of the second molar (tooth #37) were 0.5 mm, 0.5 mm, and 0 mm, respectively (Figure 1B and C), as revealed by clinical observation.

Laboratory examinations
No abnormality found in laboratory examination

Imaging examinations
Cone beam computed tomography showed good osseointegration around the implant, which suggested that the implant placement was successful (shown in Figure 1A).

FINAL DIAGNOSIS
Buccal keratinized gingiva insufficiency of tooth #37.

TREATMENT
To avoid inflammation, we planned to perform stage II surgery after obtaining sufficient keratinized gingiva. There were two surgical plans for the patient to choose, ARF + FGG surgery, and ARF + XCM + PRF surgery. The patient was informed of the procedure and risks, and she preferred the second method as she was afraid of pain and infection, and written informed consent for surgery was obtained.

Therefore, an ARF technique correlated with XCM and PRF was performed to increase the reduced keratinized tissue width and thickness, while patient morbidity was reduced by avoiding a second site. Before the surgery, the operative risk and complications were communicated with the patient, and the informed written consent was obtained from the patient for the operation and publishing of the case report. Next, the patient rinsed with mouth 0.12% chlorhexidine for three times. After local infiltration anesthesia by using articaine, a linear incision that deviated lingually was made, as showed Figure 2A. As it was impacted by buccal muco-gingival movement, the buccal full-thickness flap was split into a semi-thick flap with a No. 15 blade (Figure 2B), and the upper flap was positioned apically with 5-0 protein absorbable sutures by a vertical mattress (Figure 2C and D). The graft procedure involved the following two steps. First, PRF with multiple growth factors was obtained by centrifugating the patient’s blood at a specific speed (Figure 3A), and it was adapted to the area (Figure 3B). This is beneficial for promoting healing and increasing the thickness of keratinized gingiva. Second, the XCM membrane (Mucograft®, Geistlich, Switzerland, 15 mm × 20 mm) was trimmed (Figure 3C) and used to cover the wound.
Figure 2 Surgery Process. A: Deviated lingual linear incision; B: The buccal full-thickness flap was split to a semi-thick flap by a No. 15 blade; C and D: The semi-thick flap was positioned apically with 5-0 protein absorbable sutures.

Figure 3 Graft materials implantation. A: Platelet rich fibrin (PRF) was obtained by blood centrifugation from the patient; B: PRF was covered over the exposed wound; C: Mucograft® (Geistlich, Switzerland, 15 mm × 20 mm); D: Mucograft® was trimmed and added to cover the wound above the PRF by suture fixation.

above the PRF (Figure 3D), when it contacted with blood, thick loosened graft material can become thin and elastic, and it is good for suture fixation. No intentions and folds were made to exert external forces on the matrix in an attempt to cover the wound surface without disturbing its tridimensional structure.

OUTCOME AND FOLLOW-UP

Following the surgery, the patient was administered antibiotics (oral administration, amoxicillin 500 mg TID, metronidazole 300 mg TID) for 3 d to prevent bacterial infection. During the first 2 wk, the patient was informed not to brush the treated area, but rather to rinse the area with 0.12% chlorhexidine mouthwash twice a day.

Three days after the operation, we observed that the edge of the wound was slightly red and swollen but without infection, the surface of the wound was covered with a pseudomembrane, and the patient had no feelings of abnormality (Figure 4A). The sutures were removed after 10 days. The patient was checked at 5 d (Figure 4B), 10 d (Figure 4C), and 1 mo (Figure 5A) after the surgery.

Over time, the grafts tended to become absorbed, and the keratinized gingiva gradually grew along the Mucograft® surface until the wound closed.

After 4 wk, the wound was well-healed and the width and thickness of the keratinized gingiva reached 4 mm (Figure 5A) and 4.5 mm (Figure 5B), which was suitable for regular stage II surgery. Finally, the keratinized gingiva around the healing abutment was healthy, adequate and consistent with adjacent tissue (Figure 6A). As indicated by the periodontal probe measurement, the width of the buccal keratinized gingiva from mesial to distal reached 4 mm, 4 mm and 3 mm, respectively (Figure 6B-D). The patient was satisfied with the final esthetic outcomes.
Figure 4 Healing process. A: 3 d; B: 7 d; C: 10 d.

Figure 5 After 4 wk, stage II surgery was performed. A: The width of the buccal keratinized gingiva of tooth #37 is 4 mm; B: The thickness of mucosa is 4.5 mm.

Figure 6 The keratinized gingiva. A: The keratinized gingiva around the healing abutment was healthy, adequate and consistent with adjacent tissue; B: The mesial width of the buccal keratinized gingiva was 4 mm; C: The middle width of the buccal keratinized gingiva was 4 mm; D: The distal width of the buccal keratinized gingiva was 3 mm.

and the discomfort level was acceptable in terms of the pain, swelling, bleeding and chewing activity during the first healing period (Table 1).
DISCUSSION

There is junctional epithelium around the dental cervix and many sharpey fibers between the cementum and alveolar bone, so nature teeth exhibit a stronger ability to defend against mechanical and bacterial stimulation. In contrast, dental implants are wrapped annularly by connective tissue, relying only on hemidesmosome connections [6]. Peri-implant gingiva is so easy to move, thereby causing peri-implantitis that is attributed to bacterial invasion[7]. From another perspective, the attached gingiva of healthy teeth is composed of keratinized gingiva. The epidermis layer of keratinized gingiva is stratified squamous epithelium, and the keratinized layer is full of keratinocytes. Epithelial nails were suggested to exist in the lamina propria. It is precisely because of this tissue structure that the mobility of the keratinized gingiva and nonkeratinized gingiva is different, and the former can better protect periodontal health[8,9].

With the extension of tooth missing time, keratinized gingiva tends to decrease, and the patients of this type should generally restore missing teeth along with keratinized gingiva augmentation. ARF is the earliest technique that has been applied to increase the keratinized gingiva around implants. The half-thick flap is opened through horizontal internal oblique incision and bilateral vertical incision, pushed apically and then sutured and fixed, so the exposed periosteal area can self-heal and form keratinized gingiva[10]. Basegmez et al [11] demonstrated that the application of ARF increased keratinized tissue by 1.15 mm at 1 year after the operation, although operation process was simple and time-saving, the postoperative tissue contraction was severe and the augmentation effect was unstable. To prevent tissue contraction, stability and curative effect predictability, clinicians attempted to combine ARF with free gingival graft (FGG) or connective tissue graft (CTG), and the research demonstrated that combined application could achieve more effective outcomes, although there are some serious shortcomings (e.g., limited autograft tissue, second operation area, risks of pain and infection, texture and color differences after the transplantation). Therefore, clinicians’ and patients’ choices should be limited to a certain extent. In the era of “patient-centered” medical treatment, while pursuing the results, the indicators of pain and satisfaction also need to be considered, therefore, clinicians are seeking an alternative to FGG or CTG[12]. Currently, acellular dermal matrix (ADM) and XCM are extensively accepted as soft tissue substitutes that are in the market. The ADM was originally applied to cover burn wounds and diabetic ulcer wounds, increase keratinized gingiva, deepen vestibular sulcus, cover dental root exposure, etc.[13]. However, as demonstrated from several clinical studies, some cases of recession occurred in the long term[14]. The other option is the XCM, a porcine absorbable XCM membrane, consisting of collagen type I and type III, a double-layer structure with one side as a porous layer for cell growth, early vascular discourse and tissue integration, and the other is a smooth and dense layer to facilitate cell adhesion and wound protection[15,16]. A randomized, controlled clinical trial by Cairo et al [17] showed that XCM and CTG obtained similar amounts of apical-coronal keratinized tissue after 6 mo, and XCM was correlated with shorter surgical time, lower postoperative morbidity, less anti-inflammatory tablet consumption and higher final patient satisfaction than those of CTG. At present, increasing the width of keratinized gingiva by ARF combined with XCM is still being explored. Biological graft substitutes are so expensive that autologous biological products can be employed to perform an economic treatment for patients, and PRF, the second generation platelet concentrate reported by Dohan et al[18] is one of the representatives, covering abundant autologous growth factors that facilitate cell proliferation and migration. Its three-dimensional (3D) fibrin network is close to the physiological state, which can promote neovascularization, and wound healing and accelerate tissue remodeling[19].

The principle of increasing keratinized gingiva of XCM refers to guiding the growth of keratinized tissue cells and fibroblasts from the edge to center by exploiting its unique 3D scaffold[20]. Therefore, the incision design should maximize the reservation of keratinized tissue, which contributes to keratinized tissue cell migration from the edge of the incision. In the case of this study, because of the severe atrophy of the buccal keratinized gingiva, the incision was slightly inclined to the lingual side, which

<table>
<thead>
<tr>
<th>Table 1 Patient satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (10 scores)</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>
means that certain keratinized tissue was reserved on both sides of the incision. Moreover, we did not use a vertical incision, just a simple oblique incision to maintain the blood supply. Most of the blood vessels in the gingiva are parallel to the gingival margin from back to front[21]. This is a modified ARF as a reference[22]. As a result of long-term edentulous, the alveolar ridge atrophied, the vestibular sulcus became shallow, and the positions of the frenulum and muscle varied and were higher, thereby increasing the difficulty of the operation. In addition, the vertical width of XCM implantation was limited. Thus, the muscle attachment was partially relaxed thereby increasing the difficulty of the operation. In addition, the vertical width of XCM was nearly 4 mm, and the patient satisfaction also reached 8 points on average (Table 1).

CONCLUSION
A modified ARF combined with XCM and PRF, as an alternative to FGG, was adopted to increase the keratinized gingiva in the posterior area in the mandible, and the outcomes were satisfactory. The width of keratinized tissue increased from 0.5 mm to 4 mm. It was demonstrated that this method could have a certain curative effect. For some cases meeting the indications, this method could be selected for soft tissue augmentation. Moreover, subsequent exploration will be conducted with a longer tracking time and more case summaries.

REFERENCES

10.1002/JPER.20-0627]


22 Carnio J, Camargo PM. The modified apically repositioned flap to increase the dimensions of attached gingiva: the single incision technique for multiple adjacent teeth. *Int J Periodontics Restorative Dent* 2006; 26: 265-269 [PMID: 16836168 DOI: 10.1038/sj.ocr.1210013]
