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ABOUT COVER
Associate Editor of World Journal of Clinical Cases, Bruno Ramos Chrcanovic, DDS, MSc, PhD, Associate Professor, Department of Prosthodontics, Malmö University, Malmö 214 21, Sweden. bruno.chrcanovic@mau.se

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EDITORIAL

New trends in treatment of muscle fatigue throughout rehabilitation of elderlies with motor neuron diseases

Ayman Mohamed

ORCID number: Ayman Mohamed 0000-0001-5092-3549.

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Abstract

Muscle fatigue is a problem in rehabilitation, particularly in elderlies and patients with motor neuron diseases. There are high contradictions in the effectiveness of the used methods to decrease muscle fatigue during rehabilitation. They mainly concentrate on increasing rest periods, decreasing training load, or using an ascending intensity of manner of exercise. The training should focus on the newly discovered sensory system of muscle fatigue because of the important role of the sensory system in driving the motor system. Thus, this editorial provides insight on using proprioceptive training to enhance the sensory system of muscle fatigue.

Key Words: Muscle fatigue; Rehabilitation; Elderlies; Motor neuron diseases

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Core Tip: Muscle fatigue is a major problem in rehabilitation. This editorial suggests the use of proprioceptive training in the management of muscle fatigue because it directly trains the sensory system of muscle fatigue which is the proprioceptors. This will enable the body to sense muscle fatigue and well respond to it. In addition, proprioceptive training can normalize and increase the firing rate of motor neurons through the renormalization of presynaptic inhibition and Ia muscle afferents. This could assist in increasing the number of calcium ions into the sarcoplasmic reticulum and skeletal muscles.

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Muscle fatigue is considered one of the most common problems that can decrease the effectiveness of any rehabilitation program, particularly in elderly[1] and patients with motor neuron diseases (MNDs)[2]. Muscle fatigue in elderly and MNDs mainly arises because of long-standing abnormalities in the neuromuscular system. These abnormalities include abnormal signals from α-motor neurons to muscles, abnormal actin-myosin links, abnormal signals from the motor cortex to α-motor neurons, abnormal motor cortex stimulation-contraction coupling in the muscle, abnormal signals from the motor cortex to α-motor neurons, and depletion of adenosine triphosphate (ATP) and calcium ions (Ca²⁺). Besides, aging causes an alteration in muscle fibers (type I muscle fibers usually change to type II) which raises the incidence of muscle fatigue throughout any physical activity. Also, MNDs cause atrophic alterations with denervation in muscle fibers. Accordingly, elderly with MNDs usually experience more alterations in muscle fibers because of the blend of aging and MNDs[1,2].

There are high contradictions in the literature on the effectiveness of used methods to decrease muscle fatigue during rehabilitation. Current interventions established to lessen muscle fatigue during the rehabilitation have mainly concentrated on increasing rest periods, decreasing the load during training, or using an ascending manner of exercise intensity as a try to recuperate muscle force to permit more quantity of calcium ions and ATP[3-5]. In contrast, other studies have demonstrated that leveling exercise intensity or gradual increasing of participation in exercise has little effect in decreasing the incidence of muscle fatigue[6,7].

Thus, the treatment of muscle fatigue should be changed to help these patients and decrease the incidence of muscle fatigue. Muscle fatigue is considered a protective mechanism of our body to prevent injury. To initiate this protective mechanism, there are specific receptors in the human body that feel the start of muscle fatigue. These receptors have been demonstrated to include mechanoreceptors and metaboreceptors. Mechanoreceptors have a superior role over metaboreceptors in detecting muscle fatigue. These mechanoreceptors are similar receptors of proprioception. There is strong evidence that proprioception is much less functioning in both elderly and patients with MNDs, which increases the assumption that decreased mechanoreceptors function and increased incidence of muscle fatigue are closely connected[1,2].

The function and sensitivity of mechanoreceptors can be boosted both morphologically and neurologically by proprioceptive exercise[8-10]. Increasing signals of mechanoreceptors increase α-motor neuron firing rate[8-10]. Thus, it is truthful to assume that including proprioceptive exercise in rehabilitation can decline the incidence of muscle fatigue. The key role of proprioceptive exercise to decrease the incidence of muscle fatigue includes that proprioceptive exercise can decrease the abnormality in the firing rate of motor neurons through the renormalization of presynaptic inhibition and α-motor afferents. This normalization of motor neuron firing rates could assist in increasing the number of calcium ions into the sarcoplasmatic reticulum and skeletal muscles. This mechanism significantly helps to improve muscle performance and decrease the incidence of muscle fatigue. Also, normalization of α-motorneurons firing rates can increase the acetylcholine amount at the neuromuscular junction to cross the synaptic cleft and leads to depolarization of the muscle cell membrane. This depolarization triggers high numbers of voltage-gated sodium channels over the muscle membrane and causes initiation of the action potential leading to an increase in the number of calcium ions into the sarcoplasmic reticulum and skeletal muscles[1,2].

Another conceivable effect of proprioceptive exercise in decreasing muscle fatigue is that it can improve oxygen supply, oxidative capacity of contracting muscles, and the amount of ATP, which are important to prevent muscle fatigue. Stimulation of skeletal muscle mechanoreceptors, mainly muscle spindles, can increase the heart rate which consequently increases the respiratory rate and oxygen saturation in blood flow. The oxygen utilization by a body organ equals the amount of blood flow timed by the arterial-venous O₂ variance (Fick principle). Consequently, increasing arterial-venous O₂ variance can enhance the muscle utilization of serum oxygen and its oxidative capacity and cell mitochondrial activity which helps to reduce the rate of muscle
Proprioceptive exercise can also affect the consequences of muscle fatigue in elderlies with MNDs. Muscle fatigue usually leads to movement and gait compensations. Proprioceptive exercise helps to correct any abnormal motor control and yields further coordinated movements with less effort due to its role in driving motor commands. Proprioceptive exercise causes morphological adjustments in muscle spindles themselves through adjusting sensory and proprioceptive signals coming from the working muscle leading to major plastic adjustments in the central nervous system and motor commands[8,10]. The possible mechanisms of enhancing muscle fatigue by proprioceptive training is illustrated in Figure 1.

CONCLUSION

The treatment of muscle fatigue, particularly in elderlies with MNDs, should be more investigated to produce more decrease in the rate of muscle fatigue. Proprioceptive exercise could be a valuable addition to any rehabilitating method performed to decrease muscle fatigue due to its role in refining α-motor neuron firing rates, elevating calcium ions into neuromuscular junctions, correcting abnormal motor commands, and adjusting movement compensations frequently arising with muscle fatigue in elderlies with MNDs.

REFERENCES


What emotion dimensions can affect working memory performance in healthy adults? A review

Tian-Ya Hou, Wen-Peng Cai

Abstract

Due to the critical roles of emotion and working memory in our daily activities, a great deal of attention has been given to how emotion influences working memory performance. Although the association between emotion and working memory is relatively well established, whether mood enhances or impairs working memory performance remains controversial. The present review provides a relatively representative overview of the research on the effect of different dimensions of emotion on working memory among healthy adults spanning a 30-year period. The findings show that the valence, arousal and motivational dimensions of emotion could all exert an impact on working memory performance. The impact of emotion on working memory might be modulated by task relevance, emotion type, working memory paradigms and individual differences. The vast majority of the studies regarding the effect of emotion on working memory performance focused on the impact of negatively valenced affect and yielded highly contradictory findings. The impacts of arousal and motivation on working memory have been less explored, and inconsistent findings have also been reported. Possible explanations are discussed. Considerable research on the effect of certain dimensions of emotion on working memory has suffered from a lack of control of other emotional dimensions, and different aspects of working memory have been investigated by various paradigms. Directions for further studies should include the exploration of specific dimensions of emotion on different aspects of working memory, with the other dimensions being well controlled.

Key Words: Working memory; Emotion; Valence; Arousal; Motivation; Review

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INTRODUCTION

Working memory is the ability to maintain and manipulate information in the mind over short periods[1] and is a core component of higher cognitive function, including learning, problem solving, decision-making, and reasoning[2]. Emotion is critical to human cognition and behavior and could either facilitate or hinder performance[3], which might be due to its relevance for survival. Although a burgeoning body of literature investigating the effect of emotion on working memory has emerged, the association of emotion with working memory and its underlying mechanisms are still poorly understood. The key question in understanding the emotion-cognition link is how emotion may affect working memory. Nevertheless, previous literature exploring this topic has not yet reached a consensus on whether emotion improves or impairs WM performance. This article aimed to provide an up-to-date overview of the effect of emotion on working memory based on different dimensional models of emotion.

Different dimensions of emotion are valued as essential in different models. In this article, we first review two main models of affect regarding the dimensions of emotion: one supports a classic view according to which valence and arousal are two main dimensions of emotion[4], and the other claims that apart from valence and arousal, the motivational dimension is another important aspect of emotion[5]. Then, we review the representative studies investigating the effect of emotion on working memory based on the two models.

One of the most prominent conceptions of emotion is the dimensional view. All emotions could be described by two or three independent dimensions[6]. The most frequently and widely applied model is the circumplex model[4]. The model suggests that all emotions could fall in a circle with valence and arousal as the horizontal and vertical axes, respectively. Valence refers to the evaluation of the pleasantness associated with the emotion and ranges from negative (unpleasant) to positive (pleasant), whereas arousal is defined as the level of emotional activation ranging from deactivated to activated[7]. Valence and arousal are associated with different neural systems[8]. Valence mainly activates the orbitofrontal cortex and is related to the mesolimbic dopamine system, while arousal mainly activates the amygdala and correlates with the mesencephalic reticular activating system[9,10]. Each emotion could be described as a linear combination of both valence and arousal. Happy, for instance, is conceptualized as an affective state that involves the combination of positive valence and moderate arousal in the neural system. The difference among emotional states lies at the extent of the activation of the two fundamental neurophysiological systems[11].

Other than the model mentioned above, a large body of literature suggests that emotion depends essentially on the activation of the two motivational systems: the appetitive system and the aversive system[12,13]. The former is activated in contexts that facilitate survival, whereas the latter is activated in dangerous and survival-threatening contexts. Although many researchers have pointed out that valence covaries with the activation of the motivational system and arousal equates to motivational intensity, these views have also received much criticism. Some theorists proposed that the two-dimensional model of emotion failed to capture all aspects of emotion.
emotion and reflect vital differences among some emotions[14]. For example, anger and fear are both located in the region of the circle with the combination of negative valence and high arousal, while they are still different. Anger is an approach-related emotion and drives individuals to remove barriers to achieving goals. Conversely, fear is an avoidance-related emotion and makes people turn away from a dangerous environment[15]. Thus, anger and fear reflect different motivational tendencies despite having the same levels of valence and arousal, which suggests motivation as another independent dimension of emotion. Later, Gable and Harmon-Jones reviewed previous literature and proposed a motivational dimension model of affect[5]. The model presented that affect low in motivational intensity broadens cognitive processes, while affect high in motivational intensity results in a general narrowing of cognitive scope, which adds to the understanding of the impact of emotion on cognitive performance.

There is emerging evidence that emotion could impact working memory performance. To the best of our knowledge, this is the first review that summarizes the evidence from previous literature on the effect of emotion on working memory among healthy adults, including both behavioral results and neuroimaging findings. Since the existing literature published in this field is vast, this review does not aim to be exhaustive but rather a relatively representative overview of the research on the effects of different dimensions of emotion on working memory.

Research investigating the influence of emotion on working memory could be categorized into two groups: Integral effect and incidental effect[16]. The integral effect examines how affective contents are processed in working memory. Specifically, the affective states are induced by the materials that are processed in the cognitive task. The incidental effect explores how affective states influence working memory performance. In this case, emotional state is induced by subjective emotional experiences that are irrelevant to the working memory task. A distinction between the incidental effect and the integral effect might be necessary in trying to investigate the effect of emotion on working memory. For example, the incidental emotional state of anger could cause approach-related behaviors, while facial anger expression might cause avoidance-related behaviors since it signals threatening information to the observer. A recent study explored whether the emotion-cognition link was influenced by the task relevance of emotion and found that task-irrelevant emotion disrupted cognitive performance, whereas task-relevant emotion facilitated performance[17].

LITERATURE REVIEW SEARCH STRATEGY

Three separate academic search engines were employed to conduct this review: ScienceDirect, Web of Science and Medline. Since this review aims to focus on the literature regarding the effect of emotion on working memory performance, the database search terms for all three search engines included “working memory or n-back or cognition” and “emotion or emotional or mood”. A total of 735 references were retrieved. The identified literature was then exported to Endnote X8, and duplicated articles were removed. The authors independently screened the remaining articles according to the titles and abstracts. The full texts were further downloaded if the reviewers thought the articles satisfied the inclusion criteria or were not sure about the suitability of the literature. The evaluation of the articles was conducted independently by the authors based on predefined criteria. Any disagreements were resolved by discussion. Ultimately, 43 studies were selected to be representative in investigating the impacts of emotion on working memory performance among healthy adults spanning a 30-year period. These representative articles are summarized in this review.

REVIEW OF RESEARCH ON THE INCIDENTAL EFFECTS OF VALENCE AND AROUSAL ON WORKING MEMORY

The vast majority of the literature has provided evidence for the effect of emotional states on working memory performance, with findings gaining serious momentum since the early 1990s. In particular, Eysenck and Calvo[18] put forward processing efficiency theory, suggesting that the impact of negative emotion on cognitive functioning might be mediated by the effects on working memory. Anxious people might pay more attention to anxiety responses irrelevant to the ongoing task, such as
negative cognition and self-preoccupation. As a consequence, this would occupy attention and consume limited working memory resources, which would further lead to reduced response accuracy and prolonged response time[18,19]. Eysenck et al[18] suggested that verbal and spatial working memory were equally impaired by negative emotion, while subsequent studies provided robust evidence to support that negative emotion impacted the two kinds of working memory unequally. Ikeda et al[20] found a significant difference between high- and low-anxiety groups in verbal working memory performance, whereas the discrepancy was not significant in spatial working memory. However, most studies have shown that negative emotion has a greater impact on spatial working memory than verbal working memory. One of these studies investigated the impact of threat-of-shock anxiety on verbal and spatial working memory through verbal and spatial n-back tasks that were well matched on difficulties. Under anxiety-inducing conditions, deficits in spatial working memory were greater than those in verbal working memory[21]. Li et al[19] employed the modified delayed-matching-to-sample task to explore the underlying neural mechanism behind the selective effects of negative emotion on spatial and verbal working memory using the event-related potential technique. Reduced central P2 amplitude and frontal late positive component were observed only in spatial working memory, suggesting the selective influence of negative emotion on spatial working memory performance. Additionally, the study postulated that the frontal lobe was a critical brain structure for the emotion–working memory interaction. A functional magnetic resonance imaging (fMRI) study conducted by Qin et al[22] similarly revealed that induced acute psychological stress resulted in reduced activity in the dorsolateral prefrontal cortex (PFC) during the verbal working memory task. Several studies explored the association between self-reported negative mood and PFC activity during the working memory task without any mood induction[23,24]. The level of negative mood was inversely correlated with PFC activity only during the verbal working memory task, and the negative association was independent of personality traits[24]. Sato et al[23] expanded the generalizability of these findings by replicating the experiment in a sample with different language backgrounds. From these studies, it is concluded that the PFC plays a critical role in the association between emotion and working memory[25,26].

In addition to these findings, many studies have focused on the effect of negative emotion on a specific aspect of working memory. A recent study pointed out that the updating capacity of working memory was disrupted after worry induction and that the detrimental effects were irrelevant to individuals’ inherent tendency to worry[27]. Xie and Zhang[28] explored whether negative mood affected working memory resolution (quality) and capacity (quantity). The results found that negative mood boosted visual working memory quality, while no significant effect on the quantity was observed, suggesting dissociable qualitative and quantitative aspects of working memory representation. However, contradictory findings were reported. Figueira et al[29] investigated the effect of negative emotional states on working memory capacity using contralateral delay activity (CDA) as a neurophysiological index of the representation of the task-relevant items held in working memory. During the unpleasant emotional state, the expected CDA increase that would occur from 2 to 4 to-be-remembered items was disrupted, suggesting that the unpleasant mood is related to reduced working memory capacity. Interestingly, positive trait affect was found to be positively associated with working memory capacity, and this positive correlation was still preserved even during an unpleasant emotional state, suggesting that personality traits might influence the effects of negative emotional states on working memory[30]. Conversely, a recent study found better working memory capacity in the context of depressogenic sentences than in neutral sentences[31]. Although most studies showed a facilitating or disruptive effect of negative emotional states on working memory, a recent study suggested that sad mood induction had no significant effect on the 2-back task[32]. Apart from negative “basic” emotions (e.g., anxiety, fear and anger), recent research has also examined the role of negative social emotions (e.g., shame and guilt) in working memory performance. Cavalera et al[33] suggested that negative social emotions were associated with impaired working memory performance.

When looking at the effect of positive emotion on working memory performance, the findings were also inconsistent. On the one hand, positive mood has been presented to have harmful consequences on working memory performance. Martin and Kerns[34] found that positive emotion had detrimental effects on verbal working memory capacity and proposed a possible explanation for the findings. Positive mood could enhance the spread of activation of items in working memory, which would reduce the ability to maintain the particular item in the focus of attention. On the other hand, there is evidence that positive emotional states could enhance working memory performance.
performance. Yang et al[35] suggested that positive affect facilitated working memory measured by the operation span task.

Some studies also compared the influence of both positive and negative emotional states on working memory. The valence model proposed that the left PFC was specialized for pleasant affect, while the right PFC was specialized for unpleasant affect. Verbal working memory was processed in the left hemisphere, whereas visuospatial working memory was based on the right hemisphere. Storbeck et al[36] reported that positive emotion and verbal working memory were goal-compatible and that negative emotion was goal-compatible with spatial working memory. Under these circumstances, cognitive effort would be minimized.

Osaka et al[37] explored the underlying neural activation behind the associations of positive and negative emotion with working memory using fMRI. Participants were required to read sentences to induce negative, neutral and positive emotional states and memorize the target words from the sentences. Different neural circuits were found to be involved in the modulation effects of positive and negative emotion on verbal working memory. Additionally, the findings indicated that negative emotion impeded working memory, while positive emotion enhanced working memory performance. Another study conducted by Storbeck and Maswood[38] showed that positive emotion (i.e., happiness) facilitated both verbal and spatial working memory capacity, while negative emotion (i.e., sadness) had no impact. The researchers reported no difference in the levels of arousal between happiness and sadness. Nevertheless, theoretically, happiness and sadness differed in both valence and arousal according to the circumplex model of affect.

Arousal, as a crucial dimension of affect, could also influence cognitive functioning. Emotional arousal disrupted the working memory process that was necessary for feature binding[39]. Findings from Esmaeili et al[40] showed that positive emotional arousal improved working memory performance. In this study, positive arousal was induced by a piece of positive film, which made it hard to distinguish the effects of valence and arousal.

Some researchers pointed out that valence and arousal seemed to work together to influence working memory performance. Kuhbandner and Zehetleitner[9] presented valence and arousal that could be dissociated in their impacts on executive function, which might explain heterogeneous findings reported in the previous literature. Findings from a recent study exploring the effects of valence and arousal on working memory based on virtual reality games suggested that higher levels of arousal and positive emotion had positive effects on working memory performance[41]. Several studies have reported individual differences in the impact of emotion on working memory performance. It has already been reported that both negative and positive emotions could enhance working memory capacity in the high-capacity group, whereas they impeded performance in the low-capacity group[42].

Aside from those findings, the effects of emotional distractors on working memory were also investigated. Based on the study by Anticevic et al[43], who utilized slow event-related fMRI, negative distractors at lower working memory load levels resulted in lower accuracy and longer response times in younger adults. The opposite findings were observed in the older group, suggesting that negative distractors mitigate older adults’ working memory performance[44,45]. For example, the study conducted by Oren et al[44] reported that negative distractors in the low load n-back task caused shorter response times among older adults. Further functional connectivity analysis showed that the amygdala, the region for emotional processing, deactivated in older adults, which might explain the mitigating effect of negative distractors in older groups. Nonetheless, Ziaei et al[46] reported a contrasting neural connection outcome. Participants were required to complete an emotional working memory task and ignore irrelevant emotional distractors with positive, negative and neutral valence. Functional connectivity analysis revealed that younger participants adopted only one network for encoding both negative and positive distractors, whereas older participants recruited two neural pathways. The findings stressed the key role of amygdala engagement in emotional working memory tasks among older adults, which is inconsistent with Oren’s findings regarding the deactivation of the amygdala[44]. Hence, age could impact the influence of emotion on working memory, although the underlying mechanisms are still controversial.

Based on the literature review above, both beneficial and disruptive effects of positive and negative emotional states on working memory performance have been reported. Due to highly contradictory findings in the previous literature, it has been difficult to conclude the effect of emotional states on working memory performance since the integral effect of emotion on working memory might be influenced by many other factors, such as age and personality traits.
Previous literature has suggested that emotional stimuli interfere with working memory. The first study to explore the impact of emotional content on working memory performance suggested that reaction times were longer for fear faces than for neutral faces during an emotional n-back task[47]. Jin et al[48] similarly investigated the impacts of emotional content on working memory and its underlying neural mechanisms. They reported that positive stimuli exerted a facilitating effect on verbal working memory performance by enhancing retention and retrieval processing, while negative stimuli impaired verbal working memory performance because of the responses avoided during retrieval. Later, another study extended these findings by investigating the impact of valence on verbal working memory performance using functional near-infrared spectroscopy (fNIRS) and electroencephalogram (EEG). Behavioral, fNIRS and EEG results showed that the influences of emotional content on working memory performance depended on the task difficulty and valence. Emotional content with a negative valence seemed to take precedence compared with that with a positive valence[49]. Working memory performance was more impaired under the negative valence condition. Recently, Plancher et al[50] revealed the impact of processing negative emotional content on attentional maintenance in working memory. Compared with neutral stimuli, negative emotional stimuli were associated with longer processing times and poorer performance, suggesting that emotional content would occupy attention and prevent the maintenance of working memory via attentional refreshing. Positive stimuli were proven to facilitate working memory performance after sleep deprivation[51].

However, Levens and Phelps[52] examined the impact of emotional content on the interference resolution of working memory tasks. The findings showed that both valence and arousal interacted with each other to facilitate working memory performance. Additionally, the authors proposed that trials with emotional words were associated with less interference than trials with neutral words. Follow-up investigations in the differential roles of valence and arousal in working memory performance provided further evidence for the interplay between valence and arousal[53]. The processing of valence and arousal was associated with two distinct neural pathways. Valence-related information was processed by a PFC-hippocampus circuit, whereas arousal-related information was related to an amygdala-hippocampus circuit, indicating separate mechanisms for valence and arousal. Valence was associated with competitions between representations of stimuli in a relatively explicit way. Arousal was a relatively automatic impact of emotion on working memory. The findings suggested that emotional stimuli enhanced working memory performance.

Compared with the research on the incidental effect of emotion, the findings with respect to the integral effect of emotion on working memory were less contradictory. It seems that positive emotional stimuli enhance working memory performance. Nonetheless, based on the existing evidence, the literature regarding the integral effect of emotion is relatively less in comparison to the incidental effect of emotion. The integral effects of emotional valence and arousal on working memory remain elusive.

The extensive body of literature has examined the incidental and integral effects of emotion on working memory separately. Only a handful of studies have explored the combined impacts of incidental and integral emotion. Rączy and Orzechowski[54] combined emotional states with emotional materials to investigate the combined effects on working memory. No combined effect of mood states and emotional content of the stimuli was presented. Significantly shorter reaction times for negative emotional contents were found regardless of the mood states. Participants performed more accurately under the induced positive mood state; however, they were less accurate when processing positive stimuli. These findings suggested that combining the effects of emotional states and stimuli could not heighten their individual effects.

The inconsistent findings regarding the influence of emotion on working memory suggest that valence and arousal might not fully explain the effects. Recently, the motivational dimensional model of affect introduced by Gable and Harmon-Jones[5] suggested that the effect of emotion on working memory might be modulated by...
motivational intensity. Evidence regarding the effect of the motivational dimension on working memory will be discussed.

In studies assessing the motivational dimension of affect, hemispheric asymmetry-based assertions have also been proposed\[55\]. Both withdrawal-related emotions and visuospatial working memory are processed in the left hemisphere, whereas both approach-related emotions and verbal working memory are processed in the right hemisphere. Performance would be enhanced if the type of emotion and type of working memory are based on the same hemisphere. Gray\[53\] provided robust evidence for a double association between verbal-spatial working memory under induced withdrawal/approach emotional states. Specifically, the approach emotional state could facilitate verbal working memory and impair spatial working memory, while withdrawal of the emotional state could enhance spatial working memory and impede verbal working memory. Happiness and fear were induced in the study to represent approach and withdrawal emotions, respectively. However, these two emotions were different in the valence and motivational dimensions. Thus, some research ignored the effect of motivation and interpreted Gray’s findings as a valence effect\[35,36\]. Previous literature has also investigated the influences of motivation on working memory through incentive manipulations with penalties and rewards. The study conducted by Szatowska et al\[56\] presented the differential impacts of reward and punishment on working memory performance. Specifically, compared with the no-incentive condition, verbal working memory performance was improved in the reward-incentive condition and hindered in the punishment-incentive condition, which is consistent with Gray\[53\]’s findings. Nonetheless, the reward-penalty technique was also widely used to induce positive-negative emotion in the literature, which also indicated that this method cannot rule out the valence effect.

However, contradictory findings cannot be neglected. Some studies pointed out that performance was impaired if emotions and tasks were processed in the same hemisphere\[16,57\]. For example, anxiety, as an affective state associated with avoidant tendency, impaired spatial but not verbal working memory performance\[57\]. Similarly, the study is also questioned since it is hard to tease apart the effects of valence and motivation by induction of anxiety.

To separate the effects of motivation and valence, a recent study included an anger condition to explore whether the influence of induced emotional states on working memory was based on valence or motivational dimensions of affect. As the study claimed, anger was the only negative emotion associated with approach motivation. The findings suggested that the motivational dimension was more effective on working memory performance than the valence dimension\[16\]. However, until recently, the effect of motivational dimensions of emotion on working memory has still received less attention. Very limited numbers of studies have explored the incidental effect of the motivational dimension on working memory. More in-depth research is needed to yield more insight into the role of the motivational dimension in working memory.

**FUTURE DIRECTIONS**

Complex behaviors involve both emotion and cognition. It is widely agreed that working memory lays the foundation for higher cognitive function. Exploring the impact of emotion on working memory could be the first step in understanding human behaviors. The review presents new insights into existing knowledge of what emotional dimension would influence working memory performance. All the aforementioned studies add knowledge to the emotion-cognition puzzle by addressing the effect of emotion on working memory from different emotional dimensions. Although there is mounting evidence for the effect of emotion on working memory, some questions remain unanswered (Table 1). Some suggestions for potential next steps were offered.

Although the studies reviewed here provided robust evidence that emotion could facilitate or hinder working memory performance, the findings are inconsistent and inconclusive. It is crucial to determine which dimensions of emotion impact working memory performance. The vast majority of the studies regarding the effect of emotion on working memory performance focused on the impact of negatively valenced affect and presented mixed findings. The impacts of arousal and motivation on working memory have been relatively less explored. As discussed, although valence, arousal and motivational dimensions of emotion were all proven to affect working memory performance\[16,53\], considerable research on the effect of a certain dimension of
emotion on working memory suffered from a lack of control of other emotional dimensions. This resulted in difficulty in distinguishing the effects of different emotional dimensions, which might account for the contradictory findings. Additionally, no study has considered all three dimensions. It is believed that the effect of emotion on working memory is easier to evaluate at the neural level since neural influence would be detectable even in the absence of a significant effect on behavioral results. Further studies should be specifically planned to explore these issues by exploring the effect of one dimension of emotion under the control of other dimensions and investigating the potential interplay among different emotional dimensions and its underlying neural substrates.

In previous literature, a certain emotion might be studied to explore the association between emotion and working memory. However, induced emotion in the laboratory might contain more than one subjective feeling. For example, it has been questioned by many researchers whether the emotion of “disgust” contains only one subject feeling. The induced disgust in many studies might be feelings of disgust mixed with anger. Although both disgust and anger are negative emotions, they are related to different motivational dimensions. Disgust is avoidant-related, while anger is an approach-related state. Hence, it is important to induce emotions effectively and accurately. Furthermore, it is interesting to note that unlike in the laboratory, the co-occurrence of different emotions is common in real life. Studies designed to explore complex emotions should also be conducted to increase generalizability.

One possible reason for the mixed findings reported in the previous literature might be the utilization of different working memory paradigms that address different aspects of working memory (e.g., updating, capacity and maintenance) and vary in sensitivity. It is possible to envisage that different emotions could facilitate certain aspects of working memory and hinder other aspects of working memory. Therefore, further investigations should clearly explain upon which aspects of working memory the studies are focused.

Regarding the role of individual variations in the association between emotion and working memory, another open issue refers to the individual differences in the impact of emotion on working memory performance. The interactions between emotion and working memory could be affected by many factors, such as age and personality. Thus, it is crucial to explore the influential factors that would impact the emotion-working memory link.

In real life, incidental and integral effects are more likely to coexist. For example, if a person is afraid of a snack, he would flee from snacks instead of other neutral materials. Thus, it is important to examine the combined effects. As discussed above, there are limited studies addressing the combined impacts of emotional states and stimuli. It would be important to investigate the combined effect on working memory performance.

Another important area of interest concerns the investigation of higher levels of affective phenomena, such as love. The key points lie in how to decode the complex emotions and induce them successfully in the laboratory. Future studies closer to real life have the potential to contribute to better understanding by exploring the effect of higher levels of emotion on working memory.

Finally, in the current review, we only summarized the studies pertaining to the effect of emotion on working memory in healthy adults. However, there are many studies exploring the association between emotion and working memory among individuals with psychopathologies (e.g., major depression, posttraumatic stress disorder, schizophrenia). Future studies could broaden the scope of the review.
CONCLUSION

In summary, the present review analyzed the association between emotion and working memory from the perspective of different dimensions of emotion, mainly focusing on the following research question: what emotion dimensions can affect working memory performance in healthy adults? The present review supports the view that emotion could influence working memory. Based on the current literature, the impact of emotion on working memory might be modulated by task relevance, emotion type, working memory task and personal characteristics.

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Quadrilateral plate fractures of the acetabulum: Classification, approach, implant therapy and related research progress

Xue-Feng Zhou, Si-Chao Gu, Wan-Bo Zhu, Jia-Zhao Yang, Lei Xu, Shi-Yuan Fang

ORCID number: Xue-Feng Zhou 0000-0001-6021-6573; Si-Chao Gu 0000-0003-4517-8550; Wan-Bo Zhu 0000-0003-3457-3432; Jia-Zhao Yang 0000-0002-7838-285X; Lei Xu 0000-0001-5583-5580; Shi-Yuan Fang 0000-0002-2121-5233.

Author contributions: Zhou XF designed, drafted, revised, submitted the manuscript and generated all the figures and tables; Gu SC designed the outline and drafted the manuscript; Zhu WB, Yang JZ and Xu L designed the outline and discussed and revised the article; Fang SY performed literature research, discussed the manuscript and coordinated the writing of the paper; all authors read and approved the final manuscript.

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Peer-review report's scientific quality classification

Core Tip: There has always been lack of a unified definition, a specialized fracture
INTRODUCTION

The incidence rate of acetabular fractures is increasing year by year with the development of the society and the gradual increase of high-energy injuries caused by traffic and construction accidents and low-energy injuries in elderly patients with osteoporosis[1]. The therapy of acetabular fractures has been subject to essential changes over the past 60 years, and it has always been a great challenge for orthopedists due to the complexity. Until the early 1960s, most acetabular fractures were treated conservatively. In 1964, the principle of acetabular operation was first described by Robert Judet and Emile Letournel, which brought revolutionary changes to the therapy of the injury[2]. To alleviate pain and early mobilization, improve functions, reduce the risk of post traumatic arthritis, etc., open reduction and internal fixation (ORIF) has been gradually recognized as the gold standard for the therapy of displaced acetabular fractures[3,4]. Letournel-Judet classification is clinically one of the most widely applied classifications of acetabular fractures. Acetabular fractures are divided into 10 types according to the acetabular both-column theory, including 5 types of simple fractures and 5 types of complex fractures[3]. Through careful research, it’s found that one of the concerns is that except simple fractures of the anterior or posterior wall, an important anatomical structure may be involved in the other 8 types of acetabular fractures, which is called the quadrilateral plate (QP). QP is located on the inner surface of the acetabulum, where the position is deep, and the bone quality is thin, and it is adjacent to a large number of peripheral nerves and blood vessels. Central dislocation of femoral head, acetabular fornix impingement and incarceration, as well as highly comminuted fractures are common in this area in case of high-energy trauma[5]. Therefore, operative exposure and operations are even more difficult than those of common acetabular fractures, which leads to some controversy about open reduction and fixation strategies of acetabular fractures involving QP, serving as the hotspot of research and discussion[6,7].

Currently, there is still no consensus on the therapy of QP fractures of the acetabulum, nor is there a systematic and determinative guideline. However, the key to the successful therapy of QP fractures of the acetabulum is to apply fracture classification methods with clinical guiding significance, appropriate operative approaches, appropriate implants and internal fixation methods. In recent years, the classification system regarding QP fractures has been gradually involved in the literature, filling some deficiencies of Letournel-Judet classification. In addition, various operative approaches and new implants for internal fixation targeting at QP fractures have been proposed in more and more reports, showing different styles and unique advantages. At the same time, new requirements have been put forward in terms of the effect, prognosis and development of various implant internal fixation techniques. The purpose of this paper is to summarize the definition, classification, operative approaches, implant internal fixation methods and related research progress of QP fractures of the acetabulum, and put forward some personal opinions, so as to provide some reference and help for clinical orthopedists in the treatment of QP fractures, and provide clues and guidance for clinical research in the future.
DEFINITION AND CLASSIFICATION

QP fractures of the acetabulum are quite challenging in acetabular fractures, which is mainly caused by the lack of a unified or clear definition, and different authors have different understandings and definitions of QP fractures of the acetabulum. White et al [8] believed that QP fractures of the acetabulum are any acetabular fractures with medial subluxation of femoral head. However, by means of clinical case observation, it can be found that acetabular fractures combined with central dislocation of the hip joint are not necessarily accompanied with QP fractures, and QP fractures are not necessarily associated with central dislocation of the hip joint. Sen et al [7] interpreted QP fractures as comminuted fractures on the quadrilateral surface of the medial acetabulum, and introduced the technique of QP fracture therapy by buttress plate. QP is located on the medial surface of the acetabular fossa and is a quadrilateral area connecting the anterior and posterior columns of the acetabulum. Therefore, it is still controversial whether QP belongs to the anterior column or the posterior column. A more reasonable view is that QP is an accessory structure of the acetabulum, but some scholars have classified it as the third column separately [9]. Farid [10] proposed another interpretation, noting that QP can be separated from the anterior column or the posterior column, either completely or incompletely. In a word, there is still no unified definition and no adequate guidelines in the existing literature, so there is considerable controversy about how to treat with this type of fractures. Some orthopedists suggest to apply specialized approaches or specific fixation methods, while others believe that the reduction of QP fractures mainly depends on the reduction of acetabular columns and QP fractures are independent of the hip stability or the development of post traumatic arthritis [11].

QP refers to the relatively flat surface of the true pelvis, which is located on the medial acetabulum and is often involved in acetabular fractures [11], but it is not taken as a separate parameter in most classification systems. In clinical practice, Judet-Letournel classification is still the most widely used classification of acetabular fractures, but both the Judet-Letournel classification and the AO classification are marked by column and wall injuries, with less consideration of QP. QP is not taken as an independent parameter, and there is a lack of unified quantitative indicators. Hirvensalo reported that QP fractures were always associated with acetabular fractures of the same type. However, in recent years, there have been simple QP fractures that cannot be summarized by the existing fracture classification systems among the cases reported by Laflamme et al [12], indicating that the current classification methods fail to evaluate the severity of QP fractures in an accurate and effective manner.

Prasartritha [13] suggested to include QP in the classification after reviewing the three-dimensional (3D) CT images of the medial surfaces of 84 acetabular fractures in research, and believed that complex acetabular fractures can be classified by the classification of the QP.

Einahal et al [11] proposed the definition of QP fractures and conducted classification by analyzing the anatomical and radiological features of QP in research. In the research, it was pointed out that QP fractures are generally simple fractures or comminuted fractures and can be separated from the anterior and posterior columns of the acetabulum completely or incompletely, and QP fractures of the acetabulum were accordingly divided into 4 types. Based on this, the definition and classification system of the QP fractures of the acetabulum in Cairo University Hospital (CUH) was put forward, which is the first classification system proposed for QP fractures of the acetabulum.

Yang et al [14] introduced the pelvic 3D CT images of 238 cases with QP fractures into computer software for pelvic modeling, and divided the line from the ischial spine to the iliopubic eminence in the QP into two parts. In the research, the fracture line involving the posterior half of the QP was Type A fracture, the fracture line involving the anterior half was Type B fracture, and the fracture lines involving both the posterior and anterior half of the QP were Type C fractures. Then, the frequency distribution image was obtained by the density distribution of the fracture lines. Finally, the Type A, Type B and Type C fractures accounted for 25%, 10% and 65% respectively according to statistics. At present, although none of the research can influence the status of Judet-Letournel classification, it supplements some deficiencies of Judet-Letournel classification to a certain extent, and advances clinical orthopedists to deepen understandings of QP fractures, so as to help them choose more appropriate operative approaches, fixation methods and implants (Figure 1).
Operative Approach

In general, QP fractures will cause medial displacement of the femoral head, or central dislocation in severe cases, resulting in protrusion of the femoral head into the pelvic cavity. If the femoral head is incarcerated, reduction is difficult to be realized by traction. It is of vital importance to reconstruct the anatomical structure of the acetabulum and femoral head, and the center of rotation of the femoral head should coincide with that of the acetabulum for normal anatomical structure. Moreover, after reduction and fixation of the QP fractures, the QP needs to counteract the inward and upward force of the femoral head. However, due to the special bone morphology, the special position and anatomical structure of the QP, the reduction and fixation of the QP fractures have always been the difficulties in trauma orthopedic operations[15].

The selection of operative approaches is very important in operative treatment, which is mainly performed pursuant to the type of QP fractures. When the QP fracture fragment is connected to the anterior column, the anterior approach can be applied, and reduction and fixation can be conducted through the screw-plate system and the anterior column. When the QP fracture fragment is connected to the posterior column, the Magic screws or posterior column screws can be used for reduction and fixation in case of available closed reduction, or screw plate can be used for fixation. For floating and comminuted fractures, an anterior and posterior combined approach can be applied for reduction and fixation[15].

To be specific, it is best to expose posterior fractures (posterior column, posterior column/posterior wall), transverse fractures involving the posterior wall, and specific transverse and T-shaped fractures by traditional posterior approaches. In these cases, ischiatic notch palpation can be employed to evaluate the fracture lines across the QP [16].

Other types, such as anterior column fractures, anterior wall fractures, anterior column and posterior half transverse fractures, combined both-column fractures and partial T-shaped fractures, can be well exposed by the ilioinguinal approach. In traditional ilioinguinal approaches, QP can be exposed directly through the medial window after the separation of the external iliac vessels and their related lymphatic vessels. Through the retrospective analysis of 13 patients with acetabular fractures involving QP, Peter[17,18] believed that classic exposure by the ilioinguinal approach is still the preferred method for the therapy of anteromedial displaced fractures of the acetabulum, which controls the displacement and comminution of the medial area and

Figure 1 The classification map of fracture in the quadrilateral plate and the frequency map of different zones affected by fractures were drawn according to the research of Yang et al[14]. A: Hemipelvis anatomy and quadrilateral plate marked by the red lined area; B: This picture shows the fracture lines of all 238 superimposed fractures; C: This picture illustrates the “corridors” in which nearly three quarters of the major fracture lines occurred; D: Coded map showing the frequency (totals, percentages) of all fractures involved in the different zones indicated in the quadrilateral plate.
the QP surface of the acetabulum with the help of the buttress plate. Wu et al.[19] applied the QP anterior dynamic plate-screw system developed by his/her team on 32 patients with acetabular fractures by the unilateral ilioinguinal approach, and verified the safety and effectiveness of the unilateral ilioinguinal approach for the therapy of complex acetabular fractures involving QP. Tosounidis et al[20] reported the mid-term efficacy of 30 cases whose acetabular fractures involving QP were reconstructed with the buttress plate/steel spring plate by the ilioinguinal approach. The results showed that the reconstruction of QP fractures of the acetabulum with the buttress plate via the ilioinguinal approach is an effective method for fixation(Figure 2).

However, in clinical practice, orthopedists always find it difficult to expose and reduce the anterior wall fractures of the acetabulum with transverse or longitudinal secondary fracture lines by the ilioinguinal approach, and the QP of the medial wall of the acetabulum cannot be exposed and reduced under direct vision. In addition, due to the limitation of the inguinal ligament, the anterior hip joint capsule and hip joint cannot be exposed via the ilioinguinal approach. To change the limitation of the ilioinguinal approach to the anterior exposure of the acetabulum, in April 2008, Farid[21] took the lead to report satisfactory efficacy in the therapy of 7 cases with acetabular fractures by the sub-ilioinguinal approach. According to the research about operative treatment of 34 patients with acetabular fractures, Qin et al[22] discussed the clinical efficacy of the therapy of acetabular fractures involving the anterior and medial walls and combined femoral neck fractures by the modified anterior sub-ilioinguinal approach without iliac osteotomy. He/she believed that the modified sub-ilioinguinal approach can maintain the integrity of the inguinal ligament and broaden the horizons of the anterior and medial walls of the acetabulum (including QP), and the anterior hip joint capsule, and the modified ilioinguinal approach was the good modification and supplement to the classic ilioinguinal approach.

As an alternative method to the medial window of the traditional ilioinguinal approach, the modified Stoppa approach has been described and used by many surgeons subsequently[23-27]. With obvious value, 80% of the QP can be displayed directly, and the application of subpubic fixation is relatively easy by this method[28]. The modified Stoppa approach can be used alone, or in combination with the transverse medial window of the ilioinguinal approach, or in combination with the subilioinguinal approach[7,26]. Its overall advantage is that the joint fractures can be released and reduced by virtue of the open fracture lines across the surface of the QP [29]. In the retrospective analysis by Andrés-Peiró et al[30], 16 cases with acetabular fractures involving QP were treated by the anterior modified Rives-Stoppa approach, and the results showed that the Stoppa approach is an effective and recommendable method, which has the advantages of easy, extensive and safe exposure and can control the fractures involving QP during operation in a bid to achieve anatomical reduction and stable fixation.

In recent years, the pararectus approach has been referred to as the alternative approach to the ilioinguinal approach and the modified Stoppa approach, which supports visualization of true and false pelvic surfaces (including the QP) via a simple approach lateral to the rectus abdominis[31,32]. Mardian et al[33] demonstrated that the pararectus approach presents better reduction of the acetabular fracture interspace than the classic ilioinguinal approach, but beyond that, there is little data on the effectiveness and safety of this approach. In the retrospective analysis, Xia et al[34] analyzed the data of 15 patients with acetabular both-column fractures combined with QP displacement treated with the pararectus lateral incision approach, and believed that the pararectus lateral incision approach can fully expose, reduce and fix the acetabular both-column fractures combined with QP fracture displacement with good efficacy.

What’s more, there are the classic Kocher-Langenbeck approach and the anterior and posterior combined approach. All the above approaches, especially the anterior approaches, possess their respective advantages and limitations, as well as corresponding indications and contraindications (as shown in Table 1). No matter what approach is applied, it should be selected flexibly based on the actual fracture conditions of the patient and the degree of familiarity of the surgeon with the operative approach.

In addition, with the promotion of minimal invasion concepts and the development of endoscopic techniques, orthopedists have started to explore the feasibility and effectiveness of pelvic or acetabular operation under the endoscope. In the anatomical research, Trulson et al[35] established complete pelvic rings on 4 cadavers endoscopically and carried out internal fixation with steel plates along the iliopectineal line from the public symphysis to the iliosacral joint, covering QP and ischiadic nerve, which verified the feasibility of fully endoscopic exposure of the pelvic brim and QP with the existing standard laparoscopic instruments. In addition, the internal fixation
### Table 1 Comparison of several classic anterior approaches for quadrilateral plate fractures

<table>
<thead>
<tr>
<th>Name</th>
<th>Advantage</th>
<th>Limitation</th>
</tr>
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<tbody>
<tr>
<td>Ilioinguinal approach</td>
<td>The surgical field is wide, and the upper part of QP can be effectively exposed through the middle window of the ilioinguinal approach, while the distal part can be touched by the fingers. It is especially suitable for acetabular fractures mainly in the anterior column and not involving the posterior wall</td>
<td>QP fractures cannot be directly seen, but can only be touched. Better reduction skills and tools are required, and it is prone to incomplete reduction. There are long incisions, large trauma, and complicated operations</td>
</tr>
<tr>
<td>Modified ilioinguinal approach</td>
<td>Femoral blood vessels are not exposed, and it is less likely to damage femoral blood vessels and nerves. There is relatively small blood loss</td>
<td>The same as above</td>
</tr>
<tr>
<td>Modified Stoppa approach</td>
<td>QP fractures can be fully seen and sufficiently exposed, so that direct reduction and fixation of QP fractures can be achieved effectively. It is especially suitable for QP fractures accompanied by medial displacement of the femoral head</td>
<td>This approach is limited in the case of acetabular fractures involving the high iliac ala or posterior column. It cannot sufficiently expose the anterior acetabulum, and cannot be used for posterior wall fracture. It is difficult to correct the rotation displacement of the posterior column acetabular fracture. It is often needed to be combined with iliac fossa approach in anterior column reduction. The screw direction is limited at the approach</td>
</tr>
<tr>
<td>Pararectus approach</td>
<td>Acetabular fractures can be handled under direct vision, and it is convenient to conduct reduction and fixation of acetabular fractures involving QP. It is closer to the fracture site than other approaches, and it is ideal for obese patients</td>
<td>It cannot well expose the fractures complicated with high suprapubic branch, iliac ala or anterior wall acetabular fractures, and the oblique incision at the iliac crest is often needed for reduction and fixation. It may cause denervation of the rectus abdominis, damaging the peritoneum. Retrograde ejaculation and erectile dysfunction may be left in male patients</td>
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QP: Quadrilateral plate.

Figure 2 Surgical treatment of acetabular fracture with central dislocation of the femoral head involving quadrilateral plate through ilioinguinal approach. A: Acetabular fracture with central dislocation of the femoral head involving the quadrilateral plate (QP); B: Acetabular top compression (seagull sign); C: QP fracture with obvious internal displacement; D: The three classic windows can be exposed by separating and protecting important anatomical structures such as the femoral vessels, femoral nerves and spermatic cord through the ilioinguinal approach; E: A window at the top of the acetabulum (shown by the yellow circle) is used to reduce the compressed articular surface at the top of the acetabulum; F: Intraoperative fluoroscopy (anterior column plate indicated by the red arrow, posterior column screw indicated by the yellow arrow).

with steel plates can be performed under the endoscope. However, it's believed that further research on reduction techniques is necessary when this technique is planned for clinical application.
IMPLANT INTERNAL FIXATION TECHNIQUE

There are many optional internal fixation devices, but the joint has a risk to be penetrated by the implant due to the deep location and thin texture of QP[36]. Severe comminution, osteoporosis and delayed fixation will cause additional technical difficulties during fixation.

Kirschner wire and screw fixation

Okelberry used screws and Kirschner wires in QP fixation in 1956 for the first time. He fixed one screw on the posterior medial acetabulum through the iliofemoral approach. Multiple screws or Kirschner wires may be needed in the case of severely comminuted fractures, but it is often difficult to achieve complete reduction or maintain better reduction. Larson[37] reported that the curative effect is satisfactory among 66% of the 6 patients, and proposed that the ability to maintain the comminuted fracture fragments is the key to the success of screw fixation. A variety of supplementary screws have been applied to strengthen traditional posterior column screws. In particular, Judet and Letournel described an additional screw channel for posterior column fixation, which extended through the edge of pelvis at the iliopectineal eminence or lay in the middle of QP. The clinical effectiveness of these screw fixation techniques has been verified by Karim et al[38] in a recent study.

Starr et al[39] reported many surgical techniques in the treatment of acetabular fractures with percutaneous screws, and proposed that Magic percutaneous screws can be applied in QP fracture fixation, but there were no related cases reported. According to their report, Magic screws can be used to treat simple QP transverse fractures, but it is difficult to use percutaneous screws for reduction and fixation in the case of comminuted and floating QP medially displaced fractures. Mouhsine et al[40] used percutaneous screws in the treatment of 18 elderly patients with transverse, “T”-shaped and double-column micro-displaced fractures. The efficacy is satisfactory in 17 cases, no complications occur, and the fractures are healed without secondary displacement and screw failure. With the advancement of 3D navigation techniques, Ruan et al[41] applied them in the treatment of acetabular fractures accompanied by QP fractures. The efficacy is satisfactory and no postoperative complications occur. However, it is generally believed that there may be technical difficulties of screw fixation or insufficient fixation effect in the case of severely comminuted fractures and osteoporosis.

Screw-plate system internal fixation

In terms of the surgical approach, there are mainly three methods of steel plate internal fixation: QP fixation from the anterior approach along the arcuate line through the anterior column (or QP fixation from the anterior approach by buttress plate fixing the posterior column), fixation from the posterior approach through the posterior column, and anterior-posterior fixation[15].

The implant internal fixation techniques mainly include the classic reconstruction plate technique with a medial support effect, and the subpubic buttress plate technique[7,42]. Kistler et al[6] applied hook-shaped reconstruction titanium plate combined with arc-shaped titanium plate vertical crossing internal fixation in the treatment of acetabular anterior column and QP fractures, and the curative effect is good, proving that QP reconstruction with buttress plate through the iliinguinal approach remains an effective fixation method for acetabular QP fracture surgery. Qureshi et al[36] proposed that the subpubic plate technique is suitable for patients with moderate displacement of the femoral head and QP entering the true pelvis, and also for periprosthetic fracture patients with well-fixed acetabular structure but moderate displacement to the true pelvis. Subpubic plates placed on a plane parallel or perpendicular to the displacement plane provide strong fixation for QP fractures, which significantly prevent secondary displacement fractures of the acetabulum. In a 10-year early observation, 450 cases have no reduction and fixation loss. Laflamme et al[43] used subpubic plates through the modified Stoppa approach in the treatment of 21 elderly patients with displaced QP fracture in a retrospective study, and the curative effect is satisfactory among 70% of the patients. It can be seen that proper surgical treatment with appropriate internal fixation techniques can still obtain satisfactory effects on elderly patients with osteoporosis, and the location of femoral head and acetabular top in the same center of rotation is highly important for the prognostic function.

Recently, Karim et al[38] proposed a new implant fixation technique for acetabular QP fixation, which is called the CUH support screw technique. This technique involves
the anterior column fracture reduction and reconstruction plate fixation (3.5 mm or 4.5 mm), in which the plate needs to be carefully placed on the edge of pelvis, and must be partially extended inward into the true pelvis (a key step for the success of this support screw technique), followed by QP reduction. QP can be reduced temporarily by pelvic reduction forceps, after which two or three screws are inserted through the plate to keep the QP fracture fragments in place by their friction force on the inner surface of QP. The number of screws can be increased based on the degree of QP comminution when this technique is used, and the direction of screws can also be adjusted according to the position of QP fracture fragments, so that the plate and screws can support the fracture as a separate unit. After the screws are tightened for the first time, screw loosening may occur due to reduction of fracture segments, so the screw must be tightened again in place finally, forming a three-point fixation between the plate and the bone. One of the advantages of this technique is that it needs no special methods or additional time-consuming steps in the reduction and fixation of QP fractures. In addition, as a new general technique, it can be effectively applied to various anterior approaches. Other advantages are as follows: It can avoid the risk of joint penetration and is suitable for severely comminuted QP fractures difficult to keep reduction. Its disadvantage is that the plate must be correctly positioned on the edge of pelvis and partially extended inward into the true pelvis, so as to insert the appropriate screws.

What is noteworthy is that in a study involving 32 patients with acetabular fractures, Wu et al[17] introduced a QP anterior dynamic plate-screw system with "QP screws" in the treatment of complex acetabular fractures involving QP through a single iliouinguinal approach, achieving the same result by different methods from the CLUY support screw technique proposed by Karim et al[38] mentioned above, and its safety and effectiveness were validated. During operation, the femoral head and QP fractures medially dislocated are first reduced by instruments or operations, and then the straight reconstruction plate is pre-bent into an S-shape or C-shape and placed along the edge of pelvis passing through the pubic region, the upper edge of QP and the iliac region. After that, they are not firmly fixed on the bone surface, but can be pressed on the bone surface during screwing with special equipment. The screw placement order should follow certain rules. First, the screws are fixed in the iliac region and pubic region to stabilize the acetabular anterior column. Then, QP screws are successively placed in the middle of the QP surface using a special method. QP screws are inserted along the edge of pelvis parallel to the QP surface, and they penetrate into the bone by only 1/3-1/2 of transverse diameter to avoid entering the joint cavity. During screwing, strong clamping force can be provided by the torsion and elastic recoil of the plate for QP screws.

Zhang et al[44] proposed a kind of novel QP anatomical plate in the treatment of displaced acetabular fractures involving QP, trying to solve the problem of difficulty in obtaining satisfactory fixation effect using conventional reconstruction plates. A total of 26 patients with QP fractures underwent QP anatomical plate fixation through the Stoppa approach. It was found by postoperative X-ray and CT scan that anatomical reduction and good reduction rates are 88.46% and 11.54%, respectively. No screw loosening is observed after operation, and all fractures are healed well. The Merle's Aubigné score is satisfactory at the end of more than 2 years of follow-up.

Peter[17] first supported the bent 7-10-hole 3.5 mm reconstruction plate at the medial QP through the anterior approach and then fixed it on the iliac ala of 13 patients with acetabular fractures involving QP, and then placed another reconstruction plate on the upper edge of the arcuate line to increase the mechanical stability of QP fixation. Some scholars used special-shaped blade plates to increase their contact area with QP, further raising the stability of QP fracture fixation. Sen et al[7] retrospectively analyzed the data of patients with comminuted fractures involving iliopectine eminence, QP and anterior column. The surgical technique included right-angle fixation of the spring plate (Allis T-type plate) and the subpubic support plate, and the vertical part of the T-type plate was fixed on the iliopectine eminence, while its horizontal part supported the QP. This technique is a little similar to that of Peter, but it solves the possible concurrent fracture at the iliopectine eminence, and also increases the contact area of the plate with the QP, thereby improving the mechanical stability of internal fixation.

Gillespie et al[45] reported that pelvic internal plate combined with pelvic external plate has a significantly better fixation effect than pelvic external plate alone in the treatment of acetabular fractures involving QP. The results showed that additional pelvic internal plate may have an apparent advantage in preventing catastrophic internal fixation failure.
Wang et al[46] compared the fixation effects among 4 different implants (subpubic reconstruction plate internal fixation, subpubic locking reconstruction plate internal fixation, anterior column reconstruction plate combined with QP screw internal fixation, and anterior column reconstruction plate combined with posterior column lag screw internal fixation) in a biomechanical study. The results of biomechanical measurement showed that anterior column reconstruction plate combined with posterior column lag screw internal fixation has the best stability in the treatment of acetabular QP fractures, followed by anterior column reconstruction plate combined with QP screw internal fixation. The above two methods are superior to subpubic locking reconstruction plate and reconstruction plate internal fixation. Moreover, these four fixation methods are all reliable.

In recent years, the use of titanium plate screws for direct QP fixation has been explored by some scholars, mainly including medial ilioischial plate[47] and subpelvic plate. The idea of direct fixation methods is to implant screws avoiding the region that cannot be implanted with screws in QP, in which the placement location of the plate and the implantation direction of the screw are special. The medial ilioischial is placed near the posterior boundary of QP, while the subpelvic plate is placed near the upper boundary of QP. Therefore, it is more difficult to directly fix QP fractures, especially those near the weak bone area. (Figure 3).

**Wire cerclage technique**

Wire cerclage combined with screw-plate fixation technique is more suitable for the fracture line between the greater saccrosciatic notch and the anterior inferior iliac spine. In related reports, there are more cases of high posterior column acetabular fracture and double-column acetabular fracture exposed through the ilioinguinal approach[48, 49]. Chen et al[49] adopted wire cerclage fixation combined with screw-plate system in the treatment of 35 cases of double-column fractures. Intertrochanteric osteotomy was performed through the radial approach, and 1-2 reconstruction plates and screws combined with wire cerclage fixation were used for treatment. As a result, the efficacy is satisfactory among all patients. Farid[10] used the steel spring plate to support the medial QP, and implanted two screws at the proximal end of the plate, while no screws were implanted at the distal end. Then the wire was passed through the hole on the plate, followed by cerclage. As a result, the effect is satisfactory in 5 cases.

**Titanium mesh technique**

Some scholars used titanium mesh combined with reconstruction plate in the treatment of complex acetabular fractures accompanied by QP comminution, achieving good effects. This technique has the following advantages: (1) Titanium mesh can be used to directly reduce multiple QP fracture fragments, and the internal fixation has a reliable effect; and (2) Titanium mesh can effectively and indirectly reduce the anterior-posterior columns of the acetabulum.

**Preoperative anatomical shaping technique**

With the increasing maturity of 3D printing, the use of preoperative anatomical shaping plates has become more and more popular, because the preoperative anatomical shaping technique and a larger coverage area offer larger-area support to QP after reduction. Taller et al[50] reported the use of a new 3.5 mm “Omega” plate in 15 cases of QP fractures, among which 12 cases have good or satisfactory postoperative radiological examination results. This kind of pre-shaping technique based on the preoperative CT examination technique and 3D printing technique perfects the preoperative anatomical shaping effect of the plate according to the hemipelvic mirror image on the unaffected side. Such a technical feature can satisfy the anatomical characteristics of any individual, which can shorten the operation time, and improve the adhesion of the implant to the bone and the fixation strength.

However, this method has a high cost, and most medical institutions and patients suffer from practical economic problems, so the clinical use of preoperative anatomical shaping QP implants is restricted to a certain extent currently. Boni et al[51] proposed that stainless steel locking calcaneal plate can cover a similar surface area to that of preoperative anatomical shaping plate, but its cost is significantly lower than that of the preoperative anatomical shaping plate based on 3D printing and CTD techniques.
DISCUSSION

In the last few decades, QP has attracted increasingly more attention [52,53]. However, scholars have different definitions of QP fractures, and there is still no systemic and effective classification for QP fractures yet. Therefore, some of the work is mentioned above to help better define QP, and some attempts made by many scholars on systemic classification of acetabular QP fractures in recent years are described. A good classification method should not only leave a clear impression to doctors in distinguishing different types of fractures, but also offer good guidance in the preoperative planning of such fractures. In addition, various methods for QP exposure and fixation have been developed. Despite many techniques for QP fracture fixation, none of them have been confirmed to be absolutely superior in clinical research. Reconstruction/elastic plate fixation remains the preferred internal fixation implant by most orthopedists in the surgical treatment of acetabular QP fractures currently, and its fixation strength and stability have also been basically recognized in related biomechanical studies.

It should be noted, however, that the screws placed parallel to the QP through the edge of pelvis originally described by Judet and Letournel have the same good or better performance in biomechanical studies than fixation strategies in all other tests [45,54-56]. An interesting but inconclusive question is the extent to which QP needs to be resolved during fracture fixation. In the acetabular fracture classification system, Judet and Letournel did not clearly distinguish QP fractures, but recognized that the fracture line passing through QP is a common feature of many fracture types. Fixation of simple fracture lines passing through QP combined with columnar fracture fixation is sufficient to achieve overall stability of fractures. The specific indications to QP fixation remain unclear in the case of independent QP fragments. Based on our understanding of the importance of the acetabular dome, such fractures need no special fixation in the absence of medial subluxation or instability of the femoral head [57-60]. This view is supported by previous studies on the non-surgical treatment outcome of acetabular fractures [37,61]. There is no femoral head subluxation in medial acetabular fractures. After conservative treatment, the functional outcome is still good even though there are displaced medial fractures. In the case of incarceration on the medial surface of acetabulum, the independent fixation of QP may be necessary. Under these circumstances, the reduction and fixation of QP are helpful for containing the displacement of fragments. In addition, the reduction of independent QP fragments can enhance the quality of reduction of adjacent columnar fractures in some cases. Further research is needed to determine the situations in which QP fixation is...
Table 2 Our recommendations for the treatment of quadrilateral plate fractures based on the Yang et al[14] classification hypothesis

<table>
<thead>
<tr>
<th></th>
<th>Ilioinguinal approach</th>
<th>Modified stoppa approach</th>
<th>Pararectus approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>Recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type B</td>
<td>Recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type C</td>
<td></td>
<td>Recommended (sometimes an iliac fossa approach can be combined)</td>
<td></td>
</tr>
</tbody>
</table>

We divided the line from the ischial spine to the iliopubic eminence in the QP into two parts (refer to Figure 1D). Type A: The fracture line involving the posterior half of the QP (refer to Figure 1D); Type B: The fracture line involving the anterior half of the QP (refer to Figure 1D); Type C: The fracture lines involving both the posterior and anterior half of the QP (refer to Figure 1D); QP: Quadrilateral plate.

CONCLUSION

In conclusion, with the development and advancement of medical technology, orthopedists have gained an increasingly deep understanding of acetabular QP fractures, and great progress has been made in the treatment of acetabular QP fractures, but acetabular QP fractures are still a major problem in traumatic orthopedics. It is necessary to have a basic and unified definition of QP fractures. At the same time, a more systematic classification method for QP fractures will benefit the preoperative planning of clinicians and offer guidance to the selection of internal fixation implants. In addition, there are diverse surgical approaches and implant internal fixation techniques for acetabular QP fractures, and they have their own advantages and disadvantages. Orthopedists need to flexibly grasp indications and choose more suitable surgical techniques and implants in clinic based on their own proficiency in surgical procedures and techniques combined with clinical commonality and individual difference of patients, so as to achieve the best therapeutic effect. According to related research results, the mainstream methods for QP fracture fixation currently are relatively reliable implant fixation. Many new techniques have begun to emerge in acetabular fractures involving QP, and we have good reasons to believe that this kind of surgery will develop towards smaller surgical trauma, shorter operation time, and more accurate and reliable intraoperative auxiliary system.
ACKNOWLEDGEMENTS

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Methylprednisolone accelerate chest computed tomography absorption in COVID-19: A three-centered retrospective case control study from China

Lan Lin, Dan Xue, Jin-Hua Chen, Qiong-Ying Wei, Zheng-Hui Huang

BACKGROUND

Based on the results of some large randomized controlled trials (RCTs) confirmed the efficacy of corticosteroids in coronavirus disease 2019 (COVID-19), corticosteroids have been included in World Health Organization guidelines, but remain controversial.

AIM

To investigate the efficacy and safety of low-to-moderate dose (30 to 40 mg/d) short-term methylprednisolone for COVID-19 patients.

METHODS

The clinical data of 70 patients diagnosed with COVID-19 who received antiviral therapy with Arbidol for 7-10 d before admission but had no obvious absorption on chest computed tomography (CT) imaging were retrospectively analyzed. Arbidol (as the control group) and methylprednisolone (as the corticosteroid group) were given respectively after admission. After treatment, chest CT was reexamined to evaluate the absorption of pulmonary lesions. Additionally, we evaluated and compared the lymphocyte count, erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), serum ferritin, lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), hypersensitive C-reactive protein (hs-CRP) and D-dimer levels, and also analyzed the incidence of toxic and side effects.

RESULTS

All patients in the corticosteroid group had varying degrees of CT absorption, which was significantly better than that in the control group (CT obvious
INTRODUCTION

As an emerging severe infectious respiratory disease, coronavirus disease 2019 (COVID-19) has caused a pandemic outbreak with a high infection rate, high mortality and general population susceptibility, which makes this disease a major threat to international health and economy[1]. In the absence of specific treatment methods and widespread mass vaccination, it is urgent to find clinically effective drugs to reduce mortality and shorter hospitalization stay. The therapeutic effect of corticosteroids in severe acute respiratory syndrome (SARS) has been confirmed before[2,3], but the use of corticosteroids in COVID-19 remains controversial due to the absence of evidence from randomized controlled trials(RCTs)[4]. Clinically, we observed that some patients who received low-to-moderate dose short-term corticosteroids had better pulmonary imaging absorption. A retrospective analysis of clinical data was conducted to explore the optimal time, dosage, and course of corticosteroids in the treatment of COVID-19, expecting to evaluate the efficacy and safety profiles of corticosteroid therapy.

MATERIALS AND METHODS

Subjects

A total of 70 hospitalized patients who were admitted to Wuhan Union Hospital, Renmin Hospital of Wuhan University Hubei General Hospital and Wuhan Jinyintan...
Hospital from January 27, 2020 to March 30, 2020 were included in this study. The inclusion criteria were as follows: (1) The patients had confirmed COVID-19 and typical radiological characteristics; and (2) The patients were treated with Arbidol Hydrochloride Tablets (hereinafter, Arbidol) for 7-10 d before admission, and no obvious absorption was found on reexamination of chest computed tomography (CT) scan. The exclusion criteria were as follows: (1) Previous rheumatic immune system related diseases and long-term use of corticosteroids; (2) Use of corticosteroids within 2 mo before admission; (3) Serious cardiovascular and cerebrovascular diseases, refractory hypertension, epilepsy or delirium, glaucoma; (4) Active gastrointestinal bleeding in the recent 3 mo; (5) Combination with bacterial infection; (6) Mild and critical types; or (7) Patients received antiviral therapy other than Arbidol before admission. We collected the clinical data of patients, including sex, age, underlying diseases, clinical symptoms, epidemiological history, radiological characteristics, laboratory tests, etc. The diagnostic criteria and clinical classification referred to the Diagnosis and Treatment Protocol for COVID-19 (Trial version 7th)[5]. The study was retrospectively analyzed and approved by the Medical Ethics Committee of Fujian Medical University Union Hospital (ethics approval No. 2020KJTXGF001) and conformed to the principles of the Declaration of Helsinki.

Therapy and groups
All patients were received routine oxygen therapy and nutritional support. Some of them continued to be treated with Arbidol (200 mg tid) as the control group, and some were treated with methylprednisolone (orally or intravenously) as the corticosteroid group. Chest CT was reexamined to evaluate the absorption of pulmonary lesions after 7-10 d therapy. Two senior radiologists evaluated the chest radiological characteristics independently and contributed to confirming the degree of absorption, which was classified as four situations: no absorption, slightly absorption, obvious absorption and progression.

Efficacy evaluation
Routine blood tests, liver and kidney function tests, hypersensitive C-reactive protein (hs-CRP) levels, erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), serum ferritin (SF), lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), and D-dimer levels were evaluated before and after treatment. Throat swab samples were collected for detecting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA by real-time reverse transcription polymerase chain reaction (RT-PCR). During the treatment, the patient’s temperature, respiration, pulse rate, blood pressure, blood glucose and oxygen saturation were closely monitored. The discharge criteria were as follows: (1) Body temperature that returned to normal for more than 3 d; (2) Respiratory symptoms that improved significantly; (3) Chest CT that showed significant improvement of acute exudative lesions; and (4) Two consecutive negative nucleic acid tests of respiratory tract specimens (sampling interval of at least 24 h).

Statistical analysis
Statistical analysis was performed using SPSS software (version 17.0). Enumeration data are represented by the number of cases and percentages. In addition, the differences in the variables between the corticosteroid group and control group were evaluated using the chi-square test or Fisher’s exact test for categorical variables. Ridit analysis was used for ranked data. Normally distributed measurement data are represented as the mean ± SD, and comparisons between groups were performed by the t test or two-factor repeated measurement analysis of variance. Nonnormally distributed data are represented by the median and mean rank, and comparisons between groups were performed by the rank-sum test. The index differences before initial medication, post initial medication and post-subsequent medication between the corticosteroid group and control group were compared by repeated-measures analysis. Spearman's correlation coefficient was used to determine the association between blood glucose variation and diabetes. P < 0.05 was considered to indicate a statistically significant difference.

RESULTS

General Characteristics of the Patients
All 70 patients were local cases in Wuhan. The general characteristics of the patients
are shown in Tables 1 and 2. There were 32 patients in the control group aged from 33 to 85 years old among whom 14 patients had underlying diseases (8 cases with of hypertension, 4 cases of type 2 diabetes, 2 cases of chronic obstructive pulmonary disease, 1 case of hyperlipidemia, 2 cases of gallstone, 1 case of kidney stone, 1 case of Parkinson’s disease, 1 case of rheumatoid arthritis and 1 case of systemic lupus erythematosus). There were 38 patients in the corticosteroid group aged from 27-91 years old among whom 15 patients had underlying diseases (8 cases of hypertension, 7 cases of type 2 diabetes, 1 case of rheumatoid arthritis, and 1 case of postoperative cervical cancer). There was no significant difference between the two groups in the gender distribution, classification, clinical symptoms or baseline data of underlying diseases ($P > 0.05$) (Tables 1 and 2). There was no significant difference between the two groups in the time of medication ($P > 0.05$) (Table 2). Since the time of admission did not conform to the normal distribution, the rank-sum test obtained $Z = -0.132$ and $P = 0.898$, suggesting that the days from the onset of illness to admission between the two groups was not statistically significant.

**Use of methylprednisolone**
The total days of methylprednisolone use in the corticosteroid group were 2-12 d, with the initial dose ranging from 24 to 80 mg. The patients in corticosteroid group were divided into the non-obvious absorption group (including no absorption, slightly absorption and progression) and obvious absorption group according to whether chest CT was obviously absorbed after medication. There was no significant difference in the course of corticosteroid therapy, total or daily corticosteroid dosage between the two groups ($P > 0.05$) (Table 3).

**Therapeutic effect evaluation**
During the treatment, the viral nucleic acid condition of the throat swab was dynamically monitored. If two consecutive nucleic acid tests of throat swab specimens (sampling interval of at least 24 h) were negative, the time of the first test turned negative was taken as the negative nucleic acid conversion time, and the time interval from the onset date to the negative nucleic acid conversion time was taken as the nucleic acid clearance time. The negative conversion rates of SARS-CoV-2 nucleic acid were 65.62% in the control group and 73.68% in the corticosteroid group before medication. The negative conversion rates of SARS-CoV-2 nucleic acid in the control group and the corticosteroid group were 93.75% and 97.37% after medication, respectively. There was no significant difference between the two groups in the negative conversion rate ($P > 0.05$) (Table 4) and total clearance time of SARS-CoV-2 nucleic acid ($P > 0.05$) (Table 5). After medication, all the patients in the corticosteroid group had varying degrees of CT absorption, with an obvious CT absorption rate of 89.47%. In contrast, 40.63% patients in the control group showed no absorption in chest CT and the CT obvious absorption rate was only 12.5%. The CT absorption degree of the corticosteroid group was significantly better than that of the control group, with a statistically significant difference ($P < 0.05$) (Table 4). None of them developed into critical type.

All the 70 patients completed the detection of peripheral blood indicators before and after medication. The results were as follows (Tables 6-9): (1) There was no significant difference in the lymphocyte count, ESR, SF, hs-CRP and IL-6 Level between the two groups. However, for the patients in the same group, the values of the above indexes varied at different time points with statistical significance (lymphocyte count: before the medication < after the medication; ESR, SF, hs-CRP and IL-6 Level: before the medication > after the medication). However, the interaction effects between the groups and time points did not exhibit significant differences. In other words, there was no significant difference in the gradient of each index. And (2) The LDH, CK-MB and D-dimer values of the two groups were significantly different (the corticosteroid group > the control group). Moreover, for the patients in the same group, the values of the above indexes varied at different time points with statistical significance (LDH, CK-MB and D-dimer levels: before the medication > after the medication). However, the interaction effects between the groups and time points also exhibited no significant differences.

**Observation of adverse reactions to corticosteroid therapy**
We observed no severe adverse reactions such as gastrointestinal bleeding, secondary severe infection, hypertension, diabetic ketoacidosis, mental disorders or electrolyte disorders during the whole corticosteroid treatment process (Table 10). There were 11 cases (28.95%) of hyperglycemia in the corticosteroid group, among which only 2
Table 1 Patient Demographic Characteristics

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Control group (n = 32)</th>
<th>Glucocorticoid group (n = 38)</th>
<th>summation</th>
<th>$\chi^2$ or Hc value</th>
<th>$P$ value</th>
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<tbody>
<tr>
<td>Gender</td>
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<td>15</td>
<td>30</td>
<td>0.389</td>
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<td></td>
<td>M 17</td>
<td>23</td>
<td>40</td>
<td></td>
<td></td>
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<tr>
<td>Underlying diseases</td>
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<td>23</td>
<td>41</td>
<td>0.131</td>
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<tr>
<td></td>
<td>Y 14</td>
<td>15</td>
<td>29</td>
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<tr>
<td>Hypertension</td>
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<td>54</td>
<td>0.154</td>
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<td></td>
<td>Y 8</td>
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<td>Type 2 diabetes</td>
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<td>31</td>
<td>59</td>
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<td></td>
<td>Y 4</td>
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<td>Severe type 12</td>
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<td></td>
<td>Y 24</td>
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<td></td>
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<tr>
<td>Polypnea</td>
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<td>54</td>
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<td></td>
<td>Y 4</td>
<td>12</td>
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<tr>
<td>Fatigue</td>
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<td>52</td>
<td>0.946</td>
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<td></td>
<td>Y 10</td>
<td>8</td>
<td>18</td>
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<tr>
<td>Muscle soreness</td>
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<td>2.924</td>
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<tr>
<td></td>
<td>Y 7</td>
<td>2</td>
<td>9</td>
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<td></td>
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<tr>
<td>Poor appetite</td>
<td>N 30</td>
<td>34</td>
<td>64</td>
<td>0.043</td>
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<td></td>
<td>Y 2</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Chest distress</td>
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<tr>
<td>Chest pain</td>
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<td>37</td>
<td>68</td>
<td>1</td>
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<td></td>
<td>Y 1</td>
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<td>2</td>
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<td>Y 1</td>
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<td>2</td>
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<tr>
<td>Throat pain</td>
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<td>69</td>
<td>0.457</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Y 1</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F: Female; M: Male.

Table 2 Comparison of age, the time of medication in the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Control group</th>
<th>Corticosteroid group</th>
<th>$t$ value</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62.84 ± 13.97</td>
<td>59.05 ± 13.95</td>
<td>1.132</td>
<td>0.262</td>
</tr>
<tr>
<td>The time of medication</td>
<td>7.66 ± 2.29</td>
<td>6.82 ± 1.84</td>
<td>1.668</td>
<td>0.101</td>
</tr>
</tbody>
</table>

patients needed short-acting insulin hypodermic injections to control blood glucose, while no elevated blood glucose was observed among patients in the control group. The Chi-square test was used to compare the incidence of elevated blood glucose between the two groups ($\chi^2 = 10.990, 28.95%$ vs $0\%, P = 0.001$). Spearman rank correlation analysis showed no significant correlation between elevated blood glucose
Table 3 The relationship between duration, dose of methylprednisolone use and CT improvement in the corticosteroid group (mean ± SD)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Non-obvious absorption group (n = 4)</th>
<th>Obvious absorption group (n = 34)</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of methylprednisolone use (d)</td>
<td>6.0 ± 2.0</td>
<td>6.44 ± 1.86</td>
<td>-0.445</td>
<td>0.659</td>
</tr>
<tr>
<td>Total methylprednisolone dose (mg)</td>
<td>210.0 ± 66.33</td>
<td>239.15 ± 86.09</td>
<td>-0.692</td>
<td>0.519</td>
</tr>
<tr>
<td>Daily methylprednisolone dose (mg)</td>
<td>35.72 ± 4.95</td>
<td>38.55 ± 13.17</td>
<td>-0.422</td>
<td>0.676</td>
</tr>
</tbody>
</table>

Table 4 The results of severe acute respiratory syndrome coronavirus 2 RNA and chest computerized tomography absorption

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Control group</th>
<th>Corticosteroid group</th>
<th>Summation</th>
<th>χ² or Hc value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2 RNA before medication</td>
<td>N</td>
<td>21</td>
<td>28</td>
<td>49</td>
<td>0.537</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>11</td>
<td>10</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>SARS-CoV-2 RNA after medication</td>
<td>N</td>
<td>30</td>
<td>37</td>
<td>67</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CT absorption degree after medication</td>
<td>No absorption</td>
<td>13</td>
<td>0</td>
<td>13</td>
<td>41.681</td>
</tr>
<tr>
<td></td>
<td>Slightly absorption</td>
<td>15</td>
<td>4</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obvious absorption</td>
<td>4</td>
<td>34</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

*There was no statistically difference in the negative conversion rate of severe acute respiratory syndrome coronavirus 2 nucleic acid between the two groups.

*There was significant difference in CT absorption degree between the two groups.

N: Negative; P: Positive; CT: Computerized tomography; No absorption: No change in inflammatory range; Slightly absorption: The range of inflammation is absorbed than before, less than 25%; Obvious absorption: The range of inflammation is absorbed than before, more than 25%.

Table 5 Comparison of the total clearance time of severe acute respiratory syndrome coronavirus 2 nucleic acid in the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Control group</th>
<th>Corticosteroid group</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The total clearance time (d)</td>
<td>22.13 ± 7.66</td>
<td>20.89 ± 7.70</td>
<td>0.667</td>
<td>0.507</td>
</tr>
</tbody>
</table>

Table 6 Comparison of laboratory results between the two groups before and after the medication (mean ± SD)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Group</th>
<th>Before the medication</th>
<th>After the medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte</td>
<td>Control group</td>
<td>1.35 ± 0.39</td>
<td>1.58 ± 0.44</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid group</td>
<td>1.34 ± 0.54</td>
<td>1.61 ± 0.62</td>
</tr>
<tr>
<td>ESR</td>
<td>Control group</td>
<td>25.22 ± 18.41</td>
<td>15.41 ± 9.67</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid group</td>
<td>25.71 ± 14.74</td>
<td>13.79 ± 8.24</td>
</tr>
<tr>
<td>LDH</td>
<td>Control group</td>
<td>171.66 ± 50.70</td>
<td>136.06 ± 36.80</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid group</td>
<td>226.13 ± 82.36</td>
<td>187.05 ± 68.53</td>
</tr>
<tr>
<td>SF</td>
<td>Control group</td>
<td>344.69 ± 209.42</td>
<td>202.22 ± 109.76</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid group</td>
<td>428.28 ± 249.29</td>
<td>255.19 ± 105.59</td>
</tr>
</tbody>
</table>

ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; SF: Serum ferritin.

and the existence of underlying diabetic diseases (r = 0.052, P = 0.668).
**Table 7** Comparison of laboratory results between the two groups before and after the medication (median)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>group</th>
<th>Before medication</th>
<th>After medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP</td>
<td>Control group</td>
<td>2.38 (1.12-10.96)</td>
<td>1.57 (1.33-3.20)</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid group</td>
<td>5.65 (1.57-22.0)</td>
<td>2.75 (0.87-9.0)</td>
</tr>
<tr>
<td>IL-6</td>
<td>Control group</td>
<td>8.29 (6.81-11.14)</td>
<td>6.60 (5.64-8.38)</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid group</td>
<td>10.30 (7.78-13.08)</td>
<td>8.21 (6.26-9.79)</td>
</tr>
<tr>
<td>CK-MB</td>
<td>Control group</td>
<td>0.60 (0.40-1.15)</td>
<td>0.60 (0.40-0.90)</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid group</td>
<td>6.0 (0.90-8.80)</td>
<td>4.25 (0.80-6.90)</td>
</tr>
<tr>
<td>D-dimer</td>
<td>Control group</td>
<td>0.80 (0.40-1.05)</td>
<td>0.54 (0.20-0.80)</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid group</td>
<td>1.14 (0.85-1.89)</td>
<td>0.89 (0.57-1.08)</td>
</tr>
</tbody>
</table>

hs-CRP: Hypersensitive C-reactive protein; IL-6: Interleukin-6; CK-MB: Creatine kinase-MB.

**Table 8** Comparison of different indicators between the two groups by repeated-measures analysis

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Group</th>
<th>Time</th>
<th>Group × Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>value</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td></td>
<td>0.013</td>
<td>0.909</td>
</tr>
<tr>
<td>ESR</td>
<td></td>
<td>0.038</td>
<td>0.846</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
<td>13.725</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SF</td>
<td></td>
<td>3.152</td>
<td>0.080</td>
</tr>
</tbody>
</table>
| ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; SF: Serum ferritin.

**Table 9** Comparison of different indicators between the two groups by using generalized linear mixed model

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Group</th>
<th>Time</th>
<th>Group × Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>value</td>
</tr>
<tr>
<td>hs-CRP</td>
<td></td>
<td>2.376</td>
<td>0.128</td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td>0.022</td>
<td>0.882</td>
</tr>
<tr>
<td>CK-MB</td>
<td></td>
<td>29.785</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>D-dimer</td>
<td></td>
<td>11.266</td>
<td>0.001</td>
</tr>
</tbody>
</table>

hs-CRP: Hypersensitive C-reactive protein; IL-6: Interleukin-6; CK-MB: Creatine kinase-MB.

**DISCUSSION**

COVID-19 is an emerging respiratory infectious disease caused by the novel SARS-CoV-2 that has declared a pandemic outbreak. SARS-CoV-2 including new variants is characterized by strong infectivity, diverse transmission routes, and non-specific clinical manifestations, and people are generally susceptible. Currently, the treatment for COVID-19 is still mainly focused on antivirals, nutritional support, respiratory support, expectorants, antiasthmatics and immune enhancement. Unfortunately, there is no specific drug to treat COVID-19\[1,4-5\]. Therefore, searching for effective treatment for COVID-19 has attracted considerable attention worldwide.

Corticosteroids offer advantages over conventional therapy for alleviating clinical symptoms, reducing mortality and improving prognosis by inhibiting excessive inflammatory responses and cytokine release and reducing systemic toxic symptoms and pulmonary exudation\[6\]. Clinical trials of dexamethasone have shown that it decrease 28-d mortality in patients with COVID-19 receiving respiratory support, but
Table 10 The adverse reaction of corticosteroids

<table>
<thead>
<tr>
<th></th>
<th>Control group, n = 32 (%)</th>
<th>Corticosteroid group, n = 38 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Secondary infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Elevated blood glucose</td>
<td>0 (0%)</td>
<td>11 (28.95%)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sever electrolyte disorders</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

has no benefit in patients not require oxygen even may be harmful[7]. A randomized clinical trial concluded that use of intravenous dexamethasone increased the number of ventilator free days over a 28-d in patients with COVID-19 and moderate or severe acute respiratory distress syndrome (ARDS)[8]. Wu et al[9] reported that in patients with ARDS due to COVID-19, a standard dose of methylprednisolone significantly reduced the risk of death by 62%.

However, corticosteroids are a "double-edged sword". On the one hand, these drugs can help reduce excessive inflammatory responses; on the other hand, they may suppress immune function and delay the clearance of SARS-CoV-2 RNA[5,10]. Whether patients with COVID-19 benefit from adjunctive corticosteroids still a debated issue. It has been reported that corticosteroids did not reduce mortality in patients with severe COVID-19 in intensive care units (ICUs)[11]. Liu et al[12] carried out their study among 137 participants with 2019-nC0V infection found no significant benefits from systemic corticosteroid therapy. Evidence even showed that mortality benefit in severely ill COVID-19 patients treated with corticosteroids from a meta-analysis of 21,350 COVID-19 patients[13]. In view of this, to make good use of the "double-edged sword" of corticosteroids to maximize the therapeutic effect while minimizing adverse effects, the timing, dosage and treatment course are of vital importance and should be carefully considered by clinicians. Few studies focused on the effects of corticosteroids on pulmonary imaging absorption in patients with COVID-19, so this study highlights this issue.

Arbidol is a non-nucleoside broad-spectrum antiviral drug that has been proven to be effective against coronavirus in vitro[14,15]. A retrospective study of 69 COVID-19 patients revealed that Arbidol treatment improved the discharge rate (33% in the -treated group vs 19% in the -untreated group) and decreased the mortality rate[16]. Arbidol treatment has been recommended as antiviral therapy according to the 7th trial version of Diagnosis and Treatment Protocol for COVID-19 released by the China’s National Health Commission: for adults, a dose of 200 mg tid for no more than 10 d is recommended[5].

In this study, a total of 70 patients with no obvious absorption on chest CT after 7-10 d of Arbidol antiviral therapy were included in strict accordance with the recommended treatment regimen. Arbidol (as the control group) and methylprednisolone (as the corticosteroid group) were given respectively after admission. There was no difference between the two groups in the time of medication (P > 0.05). All patients in the corticosteroid group had varying degrees of CT absorption, and the CT absorption degree in the corticosteroid group was significantly better than that in the control group (CT obvious absorption rate: 89.47% vs 12.5%, P < 0.05). In the corticosteroid group, there was no significant difference in the course of treatment, total dosage and daily corticosteroid dosage between the patients with obvious CT absorption and those without obvious CT absorption (P > 0.05), indicating that there was no difference in the corticosteroid dosage and medication time between 34 patients with obvious CT absorption and 4 patients with slight absorption.

The average daily methylprednisolone dose of the 34 patients with significant improvement in chest CT was (38.55 ± 13.17) mg, and the average course of methylprednisolone use was (6.44 ± 1.86) d; thus, this could be regarded as a low-to-moderate dose short-term regimen. There was no significant difference in the negative conversion rate and total clearance time of SARS-CoV-2 nucleic acid between the corticosteroid group and the control group (P > 0.05), indicating that the corticosteroid regimen did not affect the clearance time of the virus.
Lymphopenia and elevated levels of LDH, hs-CRP, D-dimer, IL-6, CK-MB, ESR and SF can be regarded as risk factors for progression or predictors of disease severity of COVID-19[9,16-23]. During the treatment, lymphocytes gradually increased and the ESR, SF, LDH, CK-MB, hs-CRP, IL-6 and D-dimer levels gradually decreased. It was suggested that both Arbidol and corticosteroids therapy can improve COVID-19 patients' condition.

In the whole treatment process of this study, we did not observe serious adverse reactions such as gastrointestinal bleeding, secondary severe infections, hypertension, diabetic ketoacidosis, mental disorders and electrolyte disorders. There were 11 cases (28.95%) of hyperglycemia in the corticosteroid group, which was statistically significant compared with the control group (0%) \((P = 0.001)\). Spearman rank correlation analysis suggested that there was no correlation between elevated blood glucose and the existence of underlying diabetic diseases, indicating that the increase in blood glucose was caused by corticosteroids. However, only 18.18% (2/11) of patients with hyperglycemia needed short-acting insulin to control blood glucose. Thus, the above corticosteroid regimen was safe. During the treatment of COVID-19 with corticosteroids, we should monitor the patients' blood glucose more closely to avoid the occurrence of life-threatening situations such as hyperosmotic hyperglycemia coma and ketoacidosis.

**CONCLUSION**

Our study showed that the chest CT absorption in the corticosteroid group was significantly better than that in the control group. Low-to-moderate dose short-term methylprednisolone treatment can promote pulmonary radiological absorption and improve the indexes of lymphocyte count, ESR, SF, LDH, CK-MB, hs-CRP, IL-6 and D-dimer levels. The corticosteroid regimen was not associated with any serious adverse reactions and did not delay the clearance time of SARS-COV-2. COVID-19 has caused a lot of morbidity and mortality worldwide, occupying more medical resources. Low-to-moderate dose short-term methylprednisolone can rapidly improve symptoms, oxygenation and pulmonary function, alleviate the patients' condition in a short term, reduce the hospital stay, avoid severe COVID-19 phases and save medical resources ultimately. Therefore, we suggest that confirmed COVID-19 patients with the common and severe types with no obvious improvement on chest CT after initial antiviral treatment with Arbidol can be treated with a low-to-moderate dose (30 to 40 mg/d) and short-term treatment (5-7 d) of methylprednisolone. A personalized regimen should be developed based on the underlying disease and infectious severity of the patient to fully demonstrate the advantages of corticosteroids in clinical use and to avoid adverse effects. Furthermore, RCTs need to be designed to further confirm the therapeutic effect of corticosteroids in the future.

**ARTICLE HIGHLIGHTS**

**Research background**

Coronavirus disease 2019 (COVID-19) has caused a pandemic outbreak with a high infection rate, high morbidity and mortality, occupying more public medical resources. Therefore, it is urgent to find effective treatment for COVID-19.

**Research motivation**

The use of corticosteroids in COVID-19 has been included in World Health Organization guidelines, but still remains controversial.

**Research objectives**

Examine the efficacy and safety of low-to-moderate dose short-term methylprednisolone on COVID-19 patients.

**Research methods**

Seventy COVID-19 patients received antiviral therapy with Arbidol for 7-10 d before admission but had no obvious absorption on chest computed tomography (CT) imaging were retrospectively analyzed. Arbidol (as the control group) and methylprednisolone (as the corticosteroid group) were given respectively after admission.
After treatment, chest CT was reexamined to evaluate the absorption of pulmonary lesions.

**Research results**

The degree of CT absorption in the corticosteroid group was significantly better than that of control group \((P < 0.05)\). The average daily dose and course of methylprednisolone in the patients with significant improvement on chest CT was \((38.55 \pm 13.17)\) mg and \((6.44 \pm 1.86)\) d respectively.

**Research conclusions**

Low-to-moderate dose short-term methylprednisolone can accelerate the chest CT imaging absorption of COVID-19.

**Research perspectives**

The protocol has been proven to be effective and safe in clinical use, it can improve the condition, reduce the hospital stay, avoid severe phases and save medical resources.

**ACKNOWLEDGEMENTS**

We would like to express our heartfelt thanks to all the medical staff at Wuhan Union Hospital, Renmin Hospital of Wuhan University Hubei General Hospital and Wuhan Jinyintan Hospital.

**REFERENCES**


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Retrospective Study

Analysis of photostimulable phosphor image plate artifacts and their prevalence

Sara Mohamed Elkhateeb, Ashwag Yagoub Aloyouny, Mohamed Mohamed Saeed Omer, Soad Mahmoud Mansour

ORCID number: Sara Mohamed Elkhateeb 0000-0002-1570-4524; Ashwag Yagoub Aloyouny 0000-0001-6759-2846; Mohamed Mohamed Saeed Omer 0000-0001-9808-3390; Soad Mahmoud Mansour 0000-0002-7250-5791.

Author contributions: Elkhateeb S designed and performed the research, reviewed the literature, contributed to the analysis, wrote and revised the manuscript; Mansour S performed the research, wrote and revised the manuscript; Aloyouny A provided clinical advice and revised the manuscript; Omer M contributed to data collection.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Princess Nourah Bint Abdulrahman University.

Informed consent statement: Clinical data were collected anonymously. Moreover, participants were not required to obtain informed consent to this study because all patients agreed to treatment, sharing clinical data, and participation in research by written consent at the very first visit at College of Dentistry.

Sara Mohamed Elkhateeb, Ashwag Yagoub Aloyouny, Soad Mahmoud Mansour, Department of Basic Dental Science, College of Dentistry, Princess Nourah bint Abdulrahman University, Riyadh 11671, Saudi Arabia

Mohamed Mohamed Saeed Omer, College of Dentistry, Princess Nourah bint Abdulrahman University, Riyadh 11671, Saudi Arabia

Corresponding author: Ashwag Yagoub Aloyouny, DDS, Doctor, Department of Basic Dental Science, Princess Nourah bint Abdulrahman University, King Khalid International Airport Road, Riyadh 11671, Saudi Arabia. ayaloyouny@pnu.edu.sa

Abstract

BACKGROUND
Digital radiography has recently been used in dentistry as a substitute for conventional film radiography worldwide. Digital imaging has many advantages and provides new possibilities for recording and interpreting radiographic data. This system uses different types of digital receptors.

AIM
To detect the frequency, type, and reasons behind the appearance of intraoral image artifacts acquired by photostimulable phosphor plates (PSP).

METHODS
This retrospective descriptive study was conducted in the oral and maxillofacial radiology unit of the dental clinics of the College of Dentistry, Princess Nourah University (PNU). All intraoral digital radiographs were acquired using (Gendex Expert DC, United States) an intraoral X-ray machine with 7 -mA, 65-kVP using a PSP system (Soredex DIGORA Optime imaging plate) and laser scanners (Soredex DIGORA Optime), which can house all sizes of reusable intraoral PSP sensor plates with image acquisition software (MIPACS Dental Enterprise viewer 3.2.2). A total of 50000 intraoral radiographs were retrieved from the clinical database from April 2018 to April 2020 to evaluate the reason, type, and solutions to these image artifacts.

RESULTS
Overall, 50000 intraoral digital radiographs were acquired in a two-year-period; that is, from April 2018 to April 2020. Of these, 3550 (7.1%) retakes were per-
formed due to the presence of image artifacts. Periapical radiographs were the most common image type of intraoral retakes (80.8%). Imaging artifacts were divided into three categories: operator, plate and scanning errors. Out of 3550 retakes, 5%, 1.37%, and 0.73% were related to operator, plate, and scanning errors, respectively. The cone cut was the most common operator error (988 images), Bite marks were the most common plate error (276 images), and delayed scanning artifacts were the most common scanning errors (145 images). The calculated kappa value for interobserver reliability was 0.99, indicating almost perfect interobserver agreement.

CONCLUSION

Our study discussed intraoral image artifacts that were characteristic of PSP, where the most common artifacts were bitemarks, image size reduction, scratches, and delayed scanning.

Key Words: Photostimulable phosphor image; Artifacts; Intraoral radiographs; Errors; Prevalence and types

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Core Tip: Digital radiography has been used widely in dentistry as a substitute to conventional film radiography. Digital radiography holds many advantages and provides a wide range of possibilities to interpret and archive radiographic images. The latter system uses different types of digital receptors, and as any recent technology, different types of image pitfalls are expected. Therefore, these pitfalls render improper diagnosis for the radiographic images. The appearance of intraoral radiographic image artifacts can be produced by using the reusable intraoral photostimulable phosphor sensor plates. Thus, recognizing these errors and defining the causes and their troubleshooting are crucial factors in making images possess great clinical impacts.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i2.437

INTRODUCTION

Digital radiography has recently been used in dentistry as a substitute for conventional film radiography worldwide. Digital imaging provides new possibilities for recording and interpreting radiographic data in a user-friendly digital way for archiving and teleradiography[1]. Digital imaging has many advantages over film-based radiography, such as real-time imaging, not needing the use of darkroom chemicals, having image manipulation tools, better archiving, and decreased patient and operator radiation exposure[2-6].

Dental radiography is provided by two main types of radiography: Conventional and digital radiography. Conventional radiography uses dental films that require chemical solutions for processing, more human resources, is time consuming, and with a higher radiation dose. This traditional type of radiography provides a permanent record of imaging without any possibility for archiving, and any error requires the retake of the radiograph, which exposes the patient to unnecessary additional radiation exposure. This is in contrast to digital radiography, which allows image manipulation to correct the visual characteristics of the image, such as contrast, brightness, and density, thus enhancing image quality without the need to retake the image. Digital radiography permits easy archiving of images and their electronic transfer between different specialties in the dental field. Digital radiographic technology uses electronic image receptors (digital sensors or plates), which are based on two main techniques in acquiring the image: A direct method using a charge-coupled device (CCD) or complementary metal oxide semiconductor (CMOS) sensors [7] that transmit the signal of the exposed plate directly over a wire with a real-time
image on the monitor or indirect method using a photostimulable phosphor storage plate (PSP), which forms a latent image when exposed to radiation. The stored energy is then transported to a computer for display using a laser scanner[8-10].

The scanning times of PSP plates vary from a few seconds to several minutes, depending on the type of laser scanner used and the spatial and contrast resolutions of the image[5]. PSP plates are available in a variety of sizes in a way similar to conventional films, so they are vulnerable to bending and scratching during handling[2,11].

Moreover, PSP plates must be handled more carefully than films because they are reusable after erasing the image[12]. PSP plates are selected by most dental practitioners because of their easy intraoral placement with little patient discomfort, as well as being cordless and resembling conventional films. This is in comparison to the more difficult intraoral placement of CCD plates, with more patient discomfort caused by the stiffness of these plates with a cord linking them to the computer even though an image can be obtained promptly by the practitioner after exposure of the plate in this system[11,12].

Digital radiography, like any evolving technology, produces a new type of image pitfall that remains a problem for clinicians in that it can be overwhelming. To the best of our knowledge, a systematic review of dental digital radiography artifacts in clinical usage has not yet been reported[13]. In addition, few studies have assessed PSP image errors using illustrative figures[14].

MATERIALS AND METHODS

This retrospective descriptive study was conducted in the oral and maxillofacial radiology unit of the dental clinics of the College of Dentistry, Princess Nourah University (PNU), where conventional film-based radiography was gradually replaced by digital radiography starting in 2018. All the intraoral digital radiographs were acquired using (Gendex Expert DC., United States) an intraoral X-ray machine with 7-mA 65-kVP using a PSP system (Soredex DIGORA Optime imaging plate) and laser scanners (Soredex DIGORA Optime), which can house all sizes of reusable intraoral PSP sensor plates with image acquisition software (MIPACS Dental Enterprise viewer 3.2.2).

The investigators retrieved all the digital intraoral periapical and bitewing radiographs that were taken and approved by the clinicians from all dental specialties in our college and with the consent of the patients from April 2018 to April 2020. We used the Medicor Imaging/MIPACS Toolkit software, which regularly detects and records all deleted radiographs due to retakes performed by all oral radiology technicians in the radiology unit with clarification of the image type. All the retakes were screened by two well-experienced oral and maxillofacial radiologists for evaluation of the present artifact type and cause, while the remaining images without errors were excluded from the study. Artifacts were classified into three categories: plate errors, scanning errors, and operator errors. First, two observers sat together in a collaboration session to determine the criteria and subtypes for each category of digital artifacts to unify the interpretation process.

The observers independently evaluated and agreed on image artifacts. When disagreement existed among them, consensus was reached through discussion. Out of the selected cases, 1000 images with errors were reevaluated by both investigators after 2 wk for the calculation of interobserver reliability. Our retrospective study was approved by the institutional review board (IRB) of PNU.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 23 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL, United States), and the frequencies and percentages of PSP artifacts were calculated. Interobserver reliability was analyzed with kappa analyses, which was interpreted as follows: P value < 0 denoted less than chance agreement, 0.01-0.20 denoted slight agreement, 0.21-0.40 denoted fair agreement, 0.41-0.60 denoted moderate agreement, 0.61-0.80 indicated substantial agreement, and 0.81-0.99 was considered almost perfect agreement[15].

RESULTS

A total of 50000 intraoral digital radiographs were acquired in the 2 year-period from
April 2018 to April 2020. Of these, 3550 (7.1%) retakes were performed due to the presence of image artifacts. Of these retakes, 5% was related to operator errors and 2.1% was related to plate and scanning errors. The calculated kappa value for interobserver reliability was 0.99, indicating almost perfect interobserver agreement.

Intraoral radiographs requiring retakes due to image artifacts included 2869 (80.8%) periapical (PA) images, 518 (14.6%) bite wing images, and 163 blank images (4.6%). Imaging artifacts were divided into three categories. Of the 3550 retakes, operator errors were the most common and were observed in 2500 images (70.4%), while plate errors were detected in 685 images (19.3%) and scanning errors in 365 images (10.3%).

**Operator errors**

In this study, the operator error category consisted of eight subtypes that were closely similar to the same error categories in conventional film radiography, as this type of artifact does not depend on the type of image receptor except for the reversed or mirror image, movement of the plate inside the packet, and double exposure in the plate either due to partial erasing of the previous image or failure of the image scanning.

The cone cut was the most common error observed in 988 images (39.5%) out of 3550 images (Figure 1A), followed by the artifacts of improper PSP placement in the mouth (30.4%), projection geometry (22.4%), unexposed plate (4.5%), movement of phosphor plate in the disposable pocket (1.6%) (Figure 1A and B), reversed image (0.8%) (Figure 1c and d), overexposed (0.6%), and plate bending (0.3%).

**Plate errors**

Bite marks were the most common error observed in 276 images (40.3%), while image size reduction was detected in 174 images (25.4%). In addition, plate scratches were detected in 19.6% of cases, with other errors being contamination of PSP (6.5%), peeling of the coat (5.7%), plate damage (2.3%), and fingerprints (0.1%)(Figures 2, 3 and 4).

**Scanning errors**

Delayed scanning artifacts (non-uniform density or bright image) were the most common errors observed in 145 images (39.9%). White (radiopaque) lines (37.2%), blank images (13.4%), black (radiolucent) lines (5.5%), and double images (incomplete or partial erasing) (4.1%) were also seen. (Table 1, Figures 5 and 6).

**DISCUSSION**

Digital intraoral imaging systems have gradually replaced film-based imaging in recent years, as this technology has many advantages over conventional imaging. Two types of receptors are used for digital intraoral radiography: solid-state sensors of either CCD or CMOS, which are used with a wire and PSP plates that are cordless. Solid-state sensors have been used for more than two decades, while systems that use PSP plates have only recently been used in clinical practice. Each receptor type has its own advantages and disadvantages[2].

PSP and CCD digital systems are preferred over traditional films because of the lower radiation dose for both patients and operators, less time needed, ability to perform image manipulation as well as enhancement without the need for retake, better archiving, and environmental friendliness.

PSP plates are more comfortable to the patient than CCD because they are cordless, more flexible, and thin, which resembles standard films. However, despite their superiority, PSP plates are more susceptible to bending and scratches, require more time for scanning, and subsequently develop more image artifacts, which consequently affects image quality[15]. In previous studies, it has been stated that 95% of PSP plates used for 10 wk (used approximately 50 times) became non-diagnostic and needed to be substituted[16,17].

Radiographic artifacts that occur with plain film radiography are well-identified and documented. However, to the best of our knowledge, few studies have reported and categorized the artifacts of PSP plates[17-21]. Most of these studies investigated them in medical radiology; however, very few studies were correlated to the dental field[14,15,20,22].

Moreover, to reduce the radiation exposure of the patient, it is clinically important to avoid the occurrence of image artifacts in order to minimize repeated radiographs, which could happen through proper understanding of the reasons and solutions for...
**Table 1 Frequency and percentage of scanning errors**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
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<tbody>
<tr>
<td>Delayed scanning</td>
<td>145</td>
<td>39.9</td>
</tr>
<tr>
<td>White lines</td>
<td>136</td>
<td>37.2</td>
</tr>
<tr>
<td>Blank</td>
<td>49</td>
<td>13.4</td>
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<tr>
<td>Black lines</td>
<td>20</td>
<td>5.5</td>
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<td>Double image</td>
<td>15</td>
<td>4.1</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>365</strong></td>
<td><strong>100</strong></td>
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</table>

**Figure 1** Periapical and bitewing radiographs show some operator errors. A: Movement of phosphor plate inside the disposable packet; B: Movement of phosphor plate in the disposable packet and plate scratch; C: Reversed image, cone cut and white line; D: Reversed image and improper plate placement.

**Figure 2** Bar chart illustrating frequency and percentage of plate errors.

Therefore, the aim of this study was to detect the type, frequency, and reasons for the occurrence of intraoral image artifacts acquired by PSP plates in our dental clinics, and to propose probable methods to avoid these image artifacts.

In the present study, the examined intraoral radiographic errors were categorized into three main categories: operator, plate, and scanning errors. Operator errors were the most common and were observed in 2500 out of 50000 intraoral images (5%) and in 70% of 3550 retakes, which is in accordance with the findings of Hui-Lin Chiu et al. 2008. regarding the increased incidence of operator errors as seen in the current study. In addition, this reflects the need for broader training of radiology technicians.

In the present study, only 0.07% of 50000 intraoral images reported in the existing study presented with movement artifacts of the PSP plate inside the disposable packet. However, in Gulsahi and Secgin study in 2016, it was recorded frequently, whereas
other studies did not report this type of artifact. It has been stated that this artifact is detected only with the Digora system, where both cardboard cover and disposable plastic envelopes should be used. While the cardboard cover is used to protect the PSP plates, they may unfortunately cause motion of the plates, resulting in these artifacts [24].

The second most common errors in the current study were plate errors that were detected in 685 intraoral images (1.37% of total images and 19.3% of retakes), followed by scanning errors seen in 365 intraoral images (0.73% of total images and 10.3% of retakes). Chiu et al. [23] 2008 reported that scanning errors were the second most common error, followed by plate errors.

In the current study, bite marks were the most common plate error subtypes observed in 276 images (40.3%).

The most probable cause of the increased incidence of bitemarks in our study is the disposable plastic packet. It is used for infection control and acts as a light barrier, but it does not provide proper safety against plate damage from bite marks, bending, or pressure. Another possible reason for plate bitemarks would be the patient unintentionally biting on the plate. Thus, the patient must be comprehensively instructed to avoid doing so before the exposure.

It was reported that pediatric periapical radiographs of primary incisors that were taken by a modified technique by making the child bite on a size 2 PSP plate to keep it in place during exposure simulating occlusal radiograph could be one of the reasons for PSP bite marks. Snap-A ray film holding devices with teeth-like edges were used. Roberts, Mol, 2004 reported that the risk of teeth biting in pediatric primary incisors can be reduced by placing “adhesive backed sponge-like pads” on each side of the
Figure 4 Periapical and bitewing radiographs show some plate errors. A: Plate scratches; B-D: image size reduction; E: Image size reduction and movement of plate inside packet.

disposable sleeve that holds the reusable size 2 plate[2].

Image size reduction artifact after scanning was reported in 174 images (25.4% of retakes) and 0.3% of all intraoral images, which can be related to scanning errors. This was also reported by various studies[20].

In the present study, PSP plate scratches were detected in 19.6% of patients, while surface contamination of PSP was seen in 6.5%. To the best of our knowledge, the actual reasons for plate surface contamination and scratches have not been completely recognized and investigated. Kalathingal et al[17] 2010 stated that the possible cause of plate surface contamination could be the adhesive utilized in the barrier sheath, which could have affected the plate before scanning. The same study found that the plates that were used in dental colleges, as in our study, were more susceptible to scratches because of the increased number of people handling the plate, especially when they were discovered after scanning and before packaging the plate with a new protective sheath. Also, Kalathingal et al[17] 2010 reported that the hard rubbing of PSP plates with alcohol could be a cause for more scratches, and recommended that only the plates with visible surface contamination should be lightly wiped to remove any contaminants[17].

In the current study, peeling of the coat was found in 5.7%, plate damage was recorded in 2.3%, and fingerprints were found in 0.1% of plates. These findings were in the line with those reported by Gulsahi and Secgin in 2016, wherein they found damaged plates to occur in only a few images[20]. The most probable causes of plate damage are tough handling of PSP plates during their placement in the mouth, extensive bending, forceful placement of the plate into the scanner, or mechanical stresses exerted by the scanner roller during scanning[15].

Scanning errors were detected in 365 images (0.73% of all intraoral images), where delayed scanning was the most common error in this type and was seen in 145 images (0.29%). Despite Gulsahi and Secgin[24] reporting 12.6% of all images exhibited non-uniform brightness in their 2016 study, Chiu et al[23] recorded 0.4% delayed scanning errors in their 2008 study.

Although PSP plates can be exposed to regular light while being uncovered and imported into the scanner, it is recommended that exposure to regular light should not exceed 10 minutes, and that the scanning procedure should not be delayed more than
Figure 5 Periapical and bitewing radiographs show some scanning errors. A and B: Non-uniformity of the image; C: bright noisy image; D: Double image due to incomplete erasing.

Figure 6 Periapical radiographs show some scanning errors. A: Multiple white lines; B: Black line; C: Blank image; D: Inhomogeneous image.

that. Otherwise, the information in the plate will fade away[24], which will lead to increased signal loss and a reduction in the signal-to-noise ratio[25,26]. It could appear as total image fading with too bright an image or non-uniform image density caused by partial exposure of PSP to excessive ambient light before scanning. In addition, fluctuating signal loss leads to a noisy image[24].
In the current study, the most common subtype of scanning error was delayed scanning (39.9% of retakes), which was comparable to the results of Çalışkan and Sumer in their study in 2017, who affirmed that the probable cause for this artifact is the elimination of the plate from its cover after radiation exposure to inhibit infection before scanning[24].

It has been reported that the higher the light intensity and the longer the exposure time, the greater the loss of plate information[27]. This was supported by the study of Ang DB in 2006, which reported that plates were not exposed to any light before scanning presented no change in image quality even after many days of storage[25,28].

The second scanning error was the presence of white lines in 136 images (37.2%), which were reported to be due to dust or dirt particles on the slim scanning opening of the scanner. This caused them to remain fixed during the scanning process or dirt on the rollers, which acted as a blockage to the laser light. Thus, resulting in production of areas devoid of signals. Therefore, the mechanical scanner transport system should be checked and cleaned regularly, with additional replacement of the belt, if necessary[15].

The black or radiolucent lines that were detected in 20 images (5.5%) were hypothesized by a previous study to have resulted from electromagnetic interfering artifacts that were caused by anything that interfered, interrupted, decreased, or limited efficient scanner performance[15,29].

Moreover, Çalışkan A and Sumer AP[26] denoted this artifact as a ridging artifact, and advocated that these black lines occurred due to fast variations in the intensity of the light of the stimulating lasers as well as the loss of harmonization between rapid scan cycles and image plate movement. It is recommended to add proper electromagnetic shielding, appropriate voltage supply, uninterrupted power supply, and regular maintenance of scanner performance to avoid the occurrence of artifacts in radiolucent lines[15].

The previously mentioned errors observed in our study could be limited by proper regular orientation and enforcement by all operators, technicians, and students of the appropriate procedures of gentle handling of the PSP plates during exposure, scanning, and after scanning. This also includes focusing on the correct light rubbing of the PSP plates only with visible surface contamination to increase their longevity and usability. Moreover, regular checkups of PSP plates should be regularly performed to check the integrity of the plates. In addition, periodic maintenance, cleaning, and calibration of scanning devices would significantly reduce the number of scanning errors. Furthermore, additional comprehensive training of radiology technicians regarding application of proper radiographic techniques using the PSP system would be very beneficial in reducing operator errors.

CONCLUSION

The use of digital imaging in dental practice has recently made a revolution in image recording and analysis. Our institution made a significant modification by digitizing all dental images recently acquired using mainly the PSP system. Our study investigated the prevalence of intraoral image artifacts in our clinics, which were characteristic of PSP plates wherein the most common artifacts were bitemarks, image size reduction, scratches, and delayed scanning. Defining the causes of these artifacts and identifying methods for preventing them are of great clinical significance. Further research on PSP artifacts for further error identification and proper handling is needed and is a process that is essential to produce superior diagnostic images needed for instituting proper dental care.

ARTICLE HIGHLIGHTS

Research background

Nowadays, digital imaging outweighs conventional imaging and has been used widely in dentistry. Digital radiography allows image manipulation to adjust the visual characteristics of the image, such as contrast, brightness, and density, thus enhancing image quality without the need to retake the image.

Research motivation

Digital imaging provides an easier, comfortable, and user-friendly way for recording
and interpreting radiographic data for archiving and teleradiography.

Research objectives
To detect the frequency, type, and reasons behind the appearance of intraoral image artifacts acquired by photostimulable phosphor plates (PSP).

Research methods
This retrospective descriptive study. A total of 50000 intraoral radiographs were retrieved from the clinical database from April 2018 to April 2020 to evaluate the reason, type, and solutions to these image artifacts. All intraoral digital radiographs were acquired using an intraoral X-ray machine with 7 mA, 65-kVP using a PSP system and laser scanners, which can house all sizes of reusable intraoral PSP sensor plates with image acquisition software.

Research results
Imaging artifacts were divided into three categories; operator, plate, and scanning errors. Out of 3550 retakes, 5%, 1.37%, and 0.73% were related to the operator, plate, and scanning errors, respectively. The cone cut was the most common operator error (988 images), Bite marks were the most common plate error (276 images), and delayed scanning artifacts were the most common scanning errors (145 images).

Research conclusions
Our study discussed intraoral image artifacts that were characteristic of PSP, where the most common artifacts were bitemarks, image size reduction, scratches, and delayed scanning.

Research perspectives
Thus, recognizing intraoral radiographic image errors and defining the causes and their trouble-shooting are crucial factors in making images possess great clinical impacts.

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14 Hildebolt CF, Couture RA, Whiting BR. Dental photostimulable phosphor radiography. Dent Clin


Retrospective Study

N6-methyladenine-modified DNA was decreased in Alzheimer’s disease patients

Shuang Lv, Xiao Zhou, Yi-Ming Li, Tao Yang, Shu-Juan Zhang, Yu Wang, Shu-Hong Jia, Dan-Tao Peng

Abstract

BACKGROUND
In recent years, the prevalence of Alzheimer’s disease (AD) has increased, which places a great burden on society and families and creates considerable challenges for medical services. N6-methyladenine (m6A) deoxyribonucleic acid (DNA) adenine methylation is a novel biomarker and is abundant in the brain, but less common in AD. We support to analyze the relationship between DNA m6A and cognition in patients with AD and normal controls (NCs) in China.

AIM
To analyze the relationship between the novel m6A DNA and cognition in patients with AD and NCs in China.

METHODS
A total of 179 AD patients (mean age 71.60 ± 9.89 years; males: 91; females: 88) and 147 NCs (mean age 69.59 ± 11.22 years; males: 77; females: 70) who were age- and sex-matched were included in our study. All subjects underwent neuropsychological scale assessment and magnetic resonance imaging examination. Apolipoprotein E (APOE) genotypes were measured through agarose gel electrophoresis.
Global m6A levels were evaluated by a MethylFlash m6A DNA Methylation ELISA Kit (colorimetric). Global m6A levels in total DNA from ten AD patients with 18F-AV-45 (florbetapir) positron emission tomography (PET) positivity and ten NCs with PET negativity were analyzed by dot blotting to determine the results.

RESULTS
Our ELISA results showed that the global m6A DNA levels in peripheral blood were different between patients with AD and NCs ($P = 0.002; < 0.05$). And ten AD patients who were PET positive and ten NCs who were PET negative also showed the same results through dot blotting. There were significant differences between the two groups, which indicated that the leukocyte m6A DNA levels were different ($P = 0.005; < 0.05$). The m6A level was approximately 8.33% lower in AD patients than in NCs (mean 0.011 ± 0.006 vs 0.012 ± 0.005). A significant correlation was found between the Montreal Cognitive Assessment score and the peripheral blood m6A level in the tested population ($r = 0.143, P = 0.01; < 0.05$). However, no relationship was found with APOE ε4 ($P = 0.633, > 0.05$). Further studies should be performed to validate these findings.

CONCLUSION
Our results show that reduced global m6A DNA methylation levels are significantly lower in AD patients than in NCs by approximately 8.33% in China.

Key Words: Alzheimer disease; N6-methyladenine; DNA; Montreal Cognitive Assessment; Apolipoprotein E; Cognitive dysfunction

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Core Tip: Although Alzheimer’s disease (AD) cannot be cured, early diagnosis and treatment can greatly improve the prognosis of AD patients. Thus, we aimed to identify biomarkers of AD that can be useful in the clinic. The diagnostic criteria for AD were strictly employed in the study. We found that N6-methyladenine (m6A) DNA adenine methylation may be a novel biomarker of AD. Twenty subjects underwent 18F-AV-45 (florbetapir) positron emission tomography to test this assertion. In addition, the global m6A DNA methylation level was also correlated with cognition level.

Citation: Lv S, Zhou X, Li YM, Yang T, Zhang SJ, Wang Y, Jia SH, Peng DT. N6-methyladenine-modified DNA was decreased in Alzheimer’s disease patients. World J Clin Cases 2022; 10(2): 448-457
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DOI: https://dx.doi.org/10.12998/wjcc.v10.i2.448

INTRODUCTION
Alzheimer’s disease (AD) is the most common form of dementia. It is a progressive neurodegenerative disease with symptoms of initial memory impairment and cognitive decline. Usually, it affects patients’ behavior, speech, visuospatial orientation and motor system[1]. Pathological tau and amyloid-β (Aβ) deposition and neurodegeneration are biomarkers of AD. Studying the biological mechanisms of cognitive symptoms and trajectories of decline is important for clinicians to be able to determine prognosis and apply precision medicine in AD patients[2]. Although the incidence of AD is increasing, the treatment is still limited in preventing, slowing, and stopping the progression of the disease[3].

Cytosine deoxynucleotides in eukaryotic genomic DNA were first found to be methylated 60 years ago[4]. DNA methylation plays a crucial role in epigenetic mechanisms, including the regulation of gene expression, transposon suppression, and epigenetic memory maintenance[5]. Previous studies have shown that 5-methylcytosine DNA methylation is important in epigenetic mechanisms[6]. Because of technical limitations, the presence of N6-methyladenine (m6A) within DNA was not
found in eukaryotes in earlier generations of studies, and as such, m6A was believed to be absent from eukaryotic genomes. However, recently, m6A was discovered in unicellular organisms, namely, Caenorhabditis elegans[7], Drosophila[8], zebrafish and mammals[9]. DNA methylation usually refers to the addition of a methyl group (CH3) to any of the four types of DNA nucleotides[10]. When methylations appear on the sixth position of the purine ring of adenine, the resulting modification is called m6A. m6A is abundant in the mammalian brain[11]. In the mammalian central nervous system, stimulus-dependent regulation of m6A was found in response to sensory experiences, learning and injury[12]. A recent study showed that m6A methylation mRNA was lower in 6-month-old familial Alzheimer’s disease mice[13]. However, the study of m6A DNA in AD patients has been less studied.

Apolipoprotein E (APOE) was first proposed as an Aβ-binding protein in the brain [14]. A study showed that normal elderly individuals with APOE ε4 homozygosity (ε4/ε4) and even the ε 4 allele have a very high risk of developing clinical AD[15,16]. APOE not only changes the protein codon but also changes the quantity of CpG dinucleotides, which are the primary sites for DNA methylation[17]. A previous study showed that DNA methylation may have a relationship with APOE and AD[18]. However, there has been no research on the relationship between m6A DNA levels and APOE. Here, we examined the relationship between m6A and APOE. The levels of m6A in patients with AD and normal controls (NCs) were determined to assess whether the m6A DNA level is a new marker of AD that can be used for early detection or diagnosis.

MATERIALS AND METHODS

Study design
Participants from the Neurology Clinic of China-Japan Friendship Hospital were enrolled from March 2018 to February 2021. Before initiation, the trial was registered at http://www.chinadrugtrials.org.cn/index.html, Unique identifier: CTR20171631. This retrospective study received institutional review board approval (Ethics ID: 2017SY51), and all subjects signed an informed consent form. The participants were independently diagnosed by Dr. Wang, Dr. Jia and Dr. Peng in accordance with the National Institute of Aging and Alzheimer’s Association for patients[19,20]. The normal standard Montreal Cognitive Assessment (MoCA) scores were considered according to education in our study. Less than 6 years of education, MoCA > 19 for the subjects was considered normal, 7-12 years of education with MoCA > 22 and more than 13 years of education with MoCA > 24[21]. A total of 179 AD patients (mean age 71.60 ± 9.89 years; males: 91; females: 88) and 147 age- and sex-matched NCs (mean age 69.59 ± 11.22 years; males: 77; females: 70) were included in our study. All the subjects underwent neuroimaging analysis [magnetic resonance imaging (MRI)], and the following neuropsychological scale assessments were used: MoCA, the Activities of Daily Living (ADL) scale, the Geriatric Depression Scale (GDS), and the Hachinski Ischemia Scale (HIS). The subjects were aged 55-85 years. The inclusion criteria for the AD group were as follows: Clinical Dementia Rating > 0.5, ADL > 20, GDS ≤ 11, and HIS < 4. The exclusion criteria were as follows: (1) Presence of cerebrovascular disease causing cognitive impairment; (2) Occurrence of other neurological diseases or severe heart, liver, kidney or other systemic diseases; (3) Presence of serious illness, receipt of benzodiazepines, or history of drug abuse or mild or severe depression; and (4) Presence of other severe mental illnesses. At the same time, non-AD patients or healthy volunteers matched by the age, sex, living environment and style of the case group were selected as the control group. There was no significant difference in sex, age or ethnicity between the AD group and the control groups.

Among them, ten AD patients who were 18F-AV-45 (florbetapir) positron emission tomography (PET) positive (mean age 69.1 ± 10.16 years; males: 4; females: 6) and ten NCs (mean age 68.6 ± 7.95 years; males: 4; females: 6) who were PET negative were included in the subsequent analysis.

DNA extraction and genotyping
A 2-mL peripheral blood sample was obtained from each patient using a standard venipuncture technique. Each sample was centrifuged to separate the plasma and white blood cells. The white blood cells were rinsed with red blood cell lysis buffer (TAKARA, Japan) and then labeled with RNAlater (Thermo, United States). All the samples were stored at -80°C until the next test. According to the manufacturer’s instructions, DNA was isolated from white blood cells using the QIAamp DNA Blood
Mini Kit (QIAGEN, Germany). An ND-1000 spectrophotometer (Nanodrop Technologies, Delaware) was used to quantify the DNA samples at 450 nm to ensure that the DNA quantity was sufficient for further experiments. The ratio of the absorbance at 260/280 nm was required to be 1.8-1.9 for the DNA samples. We determined the precise length of genomic DNA by gel electrophoresis using 1% agarose gels. The DNA concentration was corrected to 100 ng/μL, and DNA samples with concentrations less than 100 ng/μL were excluded. Then, the genotyping of the APOE SNPs rs7412 and rs429358 was performed by agarose gel electrophoresis.

Quantification of the m6A DNA level
Global m6A levels in total DNA were measured using the MethylFlash m6A DNA Methylation ELISA Kit (colorimetric) (Epigentek, United States) by adding 200 ng of DNA extracted from human peripheral blood. All the experimental details followed the manufacturer’s instructions. The absolute amount of m6A in each sample was calculated by using a standard curve generated by plots of the absorbance of the positive and negative controls. m6A% indicates the ratio of m6A to total DNA.

Dot blotting
DNA that was previously corrected to 100 ng/μL before was spotted onto a nylon membrane (Bio-Rad, United States), with 1 μL of DNA in each sample, and allowed to air dry. DNA was ultraviolet (UV) crosslinked to the membrane, and the membranes were blocked for 1 h in 3% nonfat dry milk in 0.1% PBS (blocking buffer) at room temperature. Then, the cells were washed with Tween-TBS (Solarbio, China) for 10 min three times. The membranes were detected by anti-m6A antibody (1:200 dilution, Abcam, United Kingdom) in 3% milk TBS at 4 °C overnight and washed three times with Tween-TBS for 10 min each time. The membranes were detected with anti-mouse IgG secondary antibodies (1:10000 dilution, Easybio, China) for 1 h at room temperature. The visual blots were finally captured using the ECL Imaging System (Merck Millipore, United States). The signals were analyzed with Fiji ImageJ software.

Statistical analysis
We first evaluated whether the data were normally distributed. Comparisons of two groups, such as the analysis of differences in baseline characteristics between the AD patients and NCs, involved independent-samples Mann-Whitney U-tests (unpaired). The data were expressed as the mean ± standard deviation (SD) if the variance between groups was similar. The analysis of the relationships with APOE genotypes was performed by the chi-square test. When the expected count was less than 5, the Fisher’s chi-square test was used instead of the chi-square test. Spearman analysis was used to assess correlations. The associations between clinical and biological characteristics and m6A DNA levels were evaluated through linear and multivariate regression analyses with adjustment for age and sex. Medians and interquartile ranges (IQRs) are reported for non-Gaussian distributed variables. All statistical analyses in our study were performed with Statistical Package for Social Sciences (SPSS) version 20 (Armonk, United States). Two-tailed P < 0.05 was considered to indicate a significant difference in all statistical analyses.

RESULTS
Leukocyte m6A DNA level is associated with AD
We determined the global m6A DNA level in peripheral blood samples from 179 AD patients and 147 NCs (shown in Figure 1). Our results showed no differences in terms of age, sex, education, body mass index, systolic blood pressure, diastolic blood pressure, smoking and drinking habits between the AD and NC groups. The raw data are shown in Table 1. Figure 1 shows that the leukocyte m6A levels were different in patients with AD and NCs. Our study showed that the m6A level was approximately 8.33% lower in the AD patients than in the NCs (mean 0.011 ± 0.006 vs 0.012 ± 0.005). Multivariate regression analysis further confirmed that the m6A level had a positive correlation with the occurrence of AD after adjustment for age and sex (P ≤ 0.01). Thus, we found that reduced leukocyte m6A DNA levels were associated with AD.

We further verified the relationship between leukocyte m6A DNA levels and AD through dot blotting. Ten AD patients who were PET positive and ten NCs who were PET negative were age- and sex-matched. There were significant differences between the two groups, which indicated that the leukocyte m6A DNA levels were different (P
Lv S et al. m6A-modified DNA was decreased in AD patients

Table 1 Characteristics of the study population

<table>
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<tr>
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<th>NC (147)</th>
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<tr>
<td>Education (yr)</td>
<td>12 (9, 15)</td>
<td>12 (9, 15)</td>
<td>11 (9, 15)</td>
<td>0.435</td>
</tr>
<tr>
<td>BMI (kg/cm²)</td>
<td>22.29 (20.16, 24.51)</td>
<td>22.27 (20.03, 24.58)</td>
<td>22.31 (20.32, 24.62)</td>
<td>0.460</td>
</tr>
<tr>
<td>Alcohol (%)</td>
<td>69 (21.66)</td>
<td>31 (17.32)</td>
<td>38 (25.85)</td>
<td>0.061</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>107 (32.82)</td>
<td>56 (31.28)</td>
<td>51 (34.69)</td>
<td>0.514</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>129 (115, 140)</td>
<td>127 (117, 138)</td>
<td>130 (113, 143)</td>
<td>0.434</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77 (69, 83)</td>
<td>75 (68, 83)</td>
<td>78 (69, 84)</td>
<td>0.265</td>
</tr>
</tbody>
</table>

 apoE (%)
ε2/2 | 1 (0.31) | 0 (0) | 1 (0.68) |
ε2/3 | 26 (7.98) | 12 (6.70) | 14 (9.52) |
ε3/3 | 195 (59.82) | 98 (43.58) | 97 (65.99) |
ε3/4 | 57 (31.84) | 32 (21.77) |
ε4/4 | 12 (6.70) | 3 (2.04) |

P < 0.01.

Baseline data are described by medians and interquartile ranges (IQRs). Two-group comparisons, such as the analysis of differences in baseline characteristics between Alzheimer’s disease and normal control, were analyzed by two independent-samples Mann-Whitney U tests (unpaired). AD: Alzheimer’s disease; NC: Normal control; SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; APOE: Apolipoprotein E; MoCA: Montreal Cognitive Assessment.

Figure 1 Global N6-methyladenine DNA level in peripheral blood samples from 179 Alzheimer’s disease patients and 147 normal controls.

AD: Alzheimer’s disease; NC: Normal control.

= 0.005; < 0.05, n = 10 people per group) (shown in Figure 2).

Leukocyte m6A DNA level is associated with MoCA score

In addition, we also analyzed the correlation between the MoCA score and peripheral blood m6A levels and found that there was a significant correlation between the two in the tested population (r = 0.143, P = 0.01; < 0.05) (shown in Figure 3). In addition, the linear regression analysis showed that the two were positively correlated, and a positive correlation still existed after adjustment for sex and age. Thus, the m6A DNA level is associated with cognition.

A reduced leukocyte m6A DNA level is not associated with APOE

The APOE genotype was detected by agarose gel electrophoresis. The results for male patients were as follows: ε2/2 (1, 0.60%), ε2/3 (13, 7.74%), ε3/3 (103, 61.31%), ε3/4 (42,
DNA methylation can affect many biological processes by changing DNA structure and topology. Recent studies have demonstrated that m6A, a novel modified form of adenine in DNA, may function as an epigenetic biomarker of DNA modification preserved in prokaryotes and eukaryotes. m6A significantly affects DNA replication, repair, virulence, and gene regulation. It can also be used to distinguish host DNA from foreign DNA and other foreign nucleic acid elements, which is important for prokaryotic immunity. However, the occurrence and biological effects of m6A methylation are still poorly understood. Therefore, we analyzed whether m6A had any effect in AD. Liu et al. showed that m6A accounts for up to 0.1%-0.2% of total adenines during early embryogenesis in zebrafish and pigs, but during embryo development, the m6A level is relatively low. Stephen J Mondo et al. showed that the high m6A level present in early-diverging fungal lineages is related to transcriptionally active genes, and the percentage of methylated adenines can be as high as 2.8% of all adenines. M6A is associated with not only nervous system development, but also neurodegenerative diseases. To our knowledge, no study has evaluated m6A DNA methylation between NCs and AD patients. In our study, we found that global m6A DNA methylation levels were higher in NCs than in AD patients. We demonstrated this result through not only a MethylFlash m6A DNA Methylation ELISA Kit but also dot blotting. The m6A level was significantly lower in...
m6A-modified DNA was decreased in AD patients.

Memory loss and cognitive impairment are the main clinical features of AD patients [1]. Next, we explored the relationship between the MoCA score and the m6A level because the MoCA is widely used to screen for dementia [31]. In clinical work, the MoCA is also used to assess the severity of cognitive impairment [32]. In our study, we showed that there was a positive correlation between the MoCA score and the m6A level, indicating that there may be a positive correlation between m6A and cognitive function. This result further validates our hypothesis that m6A is associated with AD. Chen et al. [33] also suggested that m6A methylation may be associated with cognitive dysfunction. Deng et al. [34] found that m6A reader protein (insulin-like growth factor 2 mRNA binding protein 2) was abnormally highly expressed in AD patients. The APOE ε4 allele is the best-characterized amyloid-β (Aβ) chaperone and is related to Aβ metabolism and tau phosphorylation [35]. ε4 carriers have brain structural and developmental abnormalities (e.g., lower cortical gray matter volume in regions particularly affected by AD) that, together with functional features (e.g., deficient neuronal maintenance and repair), increase their vulnerability to neuropathological changes and subsequent late-life cognitive decline. ε4 allele insertion in mice causes tau accumulation [36]. A randomized trial showed that the amelioration of cognitive function among people aged over 65 years may occur through reducing the Ca:Mg ratio, which is mediated by reductions in 5-mC levels in APOE [37]. However, the biological mechanisms through which the ε4 allele contributes to disease pathophysiology are incompletely understood. Therefore, we hypothesized that APOE would also be related to the m6A level. However, no relationship was found (P = 0.633; > 0.05). Another study showed that compared with males, females have a higher risk of AD [38]. Thus, we further assessed whether APOE allele status had any relationship with m6A levels in females. However, no relationship was found in the female subgroup or the total group. Some limitations of our study should be noted. First, the sample size of the study was small. In addition, we did not conduct a large sample size or conduct a multicenter study, which may have caused bias in the results, such as gender bias and age bias. We concluded that the m6A level was correlated with the overall level of cognition but did not further analyze the correlation between the m6A level and various aspects of cognition (e.g., memory, executive function, visual space). Further studies are required to validate these findings.

CONCLUSION

The above study and analysis showed that the m6A level was significantly correlated with the incidence of AD. We conducted a linear regression analysis to determine the relationship between the m6A level and AD, which showed a positive correlation. The m6A level was approximately 8.33% lower in AD patients than in NCs. We will further study the effect of the m6A level on the pathological mechanisms of AD to elucidate its role in the disease.

ARTICLE HIGHLIGHTS

Research background

Alzheimer’s disease (AD) is the most common form of dementia and places a large burden on both society and family members. Extracellular senile plaques composed of amyloid-beta (Aβ) peptide and intracellular tau-containing neurofibrillary tangles in the brain are the classical view of AD pathogenesis.

Research motivation

Currently, targeting Aβ and tau-containing neurofibrillary tangles fails to stop the progression of AD. Studies have shown that early diagnosis and treatment are beneficial for improving the prognosis of AD patients. Thus, it is important to identify AD biomarkers.
Research objectives
This study aimed to determine the relationship between the novel m6A DNA and cognition in patients with AD and normal controls (NCs) in China. Complete the biomarkers of AD in clinical.

Research methods
The study included 179 AD patients and 147 NCs who were age- and sex-matched. All of them underwent neuropsychological scale assessment and magnetic resonance imaging examination. Blood samples were obtained from each subject to analyze apolipoprotein E (APOE) genotypes and global m6A levels. Global m6A levels were evaluated by a MethylFlash m6A DNA ELISA Kit (colorimetric). In addition, m6A levels from ten AD patients with 18F-AV-45 (florbetapir) positron emission tomography (PET) positivity and ten NCs with PET negativity were analyzed by dot blotting.

Research results
The study showed that the m6A level was approximately 8.33% lower in AD patients than in NCs. Multivariate regression analysis further confirmed that the m6A level had a positive correlation with the occurrence of AD ($P \leq 0.01$). The correlation between the MoCA score and peripheral blood m6A levels revealed that there was a significant correlation between the two in the tested population ($r = 0.143, P = 0.01; < 0.05$). However, m6A levels were not associated with APOE.

Research conclusions
The study showed that leukocyte m6A DNA levels are associated with AD and MoCA scores. Global m6A DNA methylation levels are significantly lower in AD patients than in NCs.

Research perspectives
We will further analyze the correlation between the m6A level and various aspects of cognition, such as memory and executive function. A further study will be performed to elucidate the effect of the m6A level on the pathological mechanisms of AD.

ACKNOWLEDGEMENTS
We thank our colleagues at Peking University, Graduate School of Peking Union Medical College and Chinese Academy of Medical Sciences, Capital Medical University and China-Japan Friendship Hospital. We thank all the staff who helped us during the study.

REFERENCES
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m6A-modified DNA was decreased in AD patients


Lv S et al. m6A-modified DNA was decreased in AD patients


Retrospective Study

Inflammation-related indicators to distinguish between gastric stromal tumors and leiomyomas: A retrospective study

Yu-Hao Zhai, Zhi Zheng, Wei Deng, Jie Yin, Zhi-Gang Bai, Xiao-Ye Liu, Jun Zhang, Zhong-Tao Zhang

ORCID number: Yu-Hao Zhai 0000-0002-3145-8933; Zhi Zheng 0000-0003-0390-9466; Wei Deng 0000-0001-5313-5599; Jie Yin 0000-0003-2708-01111; Zhi-Gang Bai 0000-0001-9234-9354; Xiao-Ye Liu 0000-0002-7557-9067; Jun Zhang 0000-0001-5411-1273; Zhong-Tao Zhang 0000-0002-4718-6821.

Author contributions: Zhai YH, Zheng Z, Deng W and Yin J designed the research study; Zhai YH performed the research; Zhai YH and Bai ZG contributed new reagents and analytic tools; Zhai YH, Liu XY, Zhang J and Zhang ZT analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Institute of Friendship Hospital, Capital Medical University Institutional Review Board.

Informed consent statement: Patients were not required to provide informed consent to the study because this was a retrospective study and only analyzed the clinical data of the patients. All patient data were analyzed after anonymization.

Conflict-of-interest statement: The

Abstract

BACKGROUND

Gastric leiomyomas and gastric stromal tumors are the most common types of gastric tumors encountered. In recent years, the incidence of the two types of tumors has been increasing, but the differential diagnosis is still a challenge in clinical work. However, as there are many reports on stromal tumors and inflammation-related indicators are gradually being paid attention to as important factors in predicting tumor prognosis, the two main purposes of this study were to explore the inflammation-related differences between the two types of tumors and to develop a nomogram as a predictive model.

AIM

To explore the differences in platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), lymphocyte mononuclear cell ratio (LMR), and SII between the two types of tumors, and simultaneously create the nomogram model.

METHODS

This study enrolled 88 patients in the gastric stromal tumor group and 56 patients in the gastric leiomyoma group, and the relevant data of the two groups were entered into the system for an integrated analysis. The primary objective of this study was to identify the differences in the inflammation index between the two types of tumors.

RESULTS

There were statistically significant differences between the two groups in sex, age, and tumor location. In comparison, gastric leiomyomas seem to be more common in women, young patients, and gastric cardia, which is in line with our previous research; the groups showed the following statistical differences: PLR (158.2% vs 134.3%, P = 0.028), NLR (2.35 vs 1.68, P = 0.000), LMR (5.75 vs 10.8, P = 0.004), and
INTRODUCTION

Gastric leiomyomas and gastrointestinal stromal tumors (GISTs) are common tumors of the gastric mucosa. It is difficult to differentiate between the two types of tumors when making the initial diagnosis. As there is at present no method available to distinguish between the two types before surgery, it can only be determined by pathology after surgery.

GISTs are the most common type of mesenchymal tumors and are mainly characterized by the expression of CD117. Stromal tumors mainly occur in the gastrointestinal tract, and 60% of GISTs occur in the stomach. GISTs may also occur on the surface of the omentum, mesentery, or peritoneum[1]. Gastric stromal tumors are low-grade malignant tumors, accounting for approximately 60%-70% of gastrointestinal tumors. Fletcher et al[2] integrated gastric stromal tumor size, mitosis, and other factors to divide the risk of gastric stromal tumor invasion into four levels: very low, low, medium, and high risk[2]. It has been used in clinical practice and is also an important tool to guide clinical work; as for medium and high-risk gastric stromal tumors, surgery is often combined with chemotherapy before and after surgery. GIST are mostly asymptomatic and often diagnosed by a physical examination. The most common clinical symptom encountered in patients with a GIST, is gastrointestinal bleeding[3]. For gastric stromal tumors, according to their location, size, and the risk of invasion, observation or surgery can be selected for treatment. Generally speaking, regular follow-up observation is sufficient for stromal tumors with diameters smaller than 2 cm. For the tumors larger than 2 cm, endoscopic or surgical treatment is determined according to the tumor’s growth status in the cavity[4,5]. Although there have been great advances in surgery and endoscopy for gastric stromal tumors, mainly focusing on the treatment of tumors less than 5 cm in size, earlier detection and a more accurate diagnosis may be of more importance to us.

SII (546.2 vs 384.3, P = 0.003). The results of the multivariate logistic regression analysis showed that sex, age, tumor location, and LMR were independent risk factors for the identification of the two types of tumors. After considering the risk factors selected by the above analysis into the predictive model, a predictive model for distinguishing gastrointestinal stromal tumors from gastric leiomyomas was established as the nomogram.

CONCLUSION

Gastric leiomyomas and gastric stromal tumors are not only different in factors such as age of the patient, but also in inflammatory indicators such as LMR and PLR. We have established a predictive model related to the laboratory indicators and are looking forward to further research conducted in this clinical area.

Key Words: Gastric leiomyoma; Gastrointestinal stromal tumor; Platelet-lymphocyte ratio; Neutrophil-lymphocyte ratio; Lymphocyte mononuclear cell ratio; SII; Nomogram

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Core Tip: We found that inflammation-related factors such as platelet-lymphocyte ratio and neutrophil-lymphocyte ratio were different in patients with gastrointestinal stromal tumors and leiomyomas, which also reflected the different inflammatory status between them. Meanwhile, this study constructed a relevant differential diagnosis model through a nomogram and evaluated its accuracy, which may be helpful for future studies.

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Gastric leiomyomas are also gastric tumors with spindle cell-like pathology, but unlike gastric stromal tumors, have no malignant potential and are a type of benign tumors. Studies have shown that gastric leiomyomas are more likely to occur in the gastric cardia— unlike GIST[6,7]. As the tumor grows, although there is no tendency to become malignant, bleeding and other symptoms occur (such as ulcers), all of which affect the patients’ quality of life. The same treatment methods are often used for gastric stromal tumors and for gastric leiomyomas, mainly because it is generally impossible to accurately distinguish the two types of tumors in the early stage. If a more accurate diagnosis could be made, the possibility of a more applicable treatment option could then be given to patients with gastric leiomyoma, and dynamic clinical observations will be more in line with current standardized diagnosis and treatment. Unlike gastric stromal tumors, leiomyomas do not have the possibility of receiving targeted therapy, and require no follow-up and observation. The quality of life and life expectancy of patients is better than that of patients diagnosed with GISTs.

Gastric tumors are often found through gastroscopy and computed tomography (CT), and then judged by the benign or malignant characteristics based on its microscopic appearance and the CT imaging; however, this is not the gold standard for diagnosis. Despite this, the differential diagnosis of the two types of tumors often cannot be reached before the pathology result is obtained. The pathology sample obtained by an endoscopy is sometimes inferior, and the support of the immunohistochemical results is needed after obtaining a pathology sample[8], which also hinders the diagnosis and treatment process of patients. Endoscopic ultrasonography is a relatively reliable examination to clarify the origin and invasion of tumors. Studies done have proven that endoscopic ultrasonography has a high accuracy rate and guiding significance for clarifying the diagnosis and assisting in the diagnosis of patients, which has provided clarification on their prognosis for many of them[9]. In addition, the application of multi-slice computed tomography (MSCT) in recent years has made the preoperative diagnosis of the two types of tumors clearer. The CT values of the tumors have been analyzed and it exposed the differences among them[10]; however, the application of these differences needs further research. The current prediction model is still flawed, and it is impossible to make an overall assessment of these tumors. Although endoscopic ultrasound can provide a hierarchical analysis, it is limited by the physician’s level of experience. The objectivity and accuracy still need to be improved via further research and clinical studies. Therefore, more objective and accessible laboratory indicators are needed to help distinguish the two types of tumors.

Inflammatory and nutritional indicators are often used to predict the prognosis of cancer patients. For malignant tumors, Balkwill et al.[11] proposed the tumor inflammatory theory, linking the occurrence and development of tumors with inflammatory factors; advances in the field of tumor research are inseparable from the discussion of the influence of its inflammatory environment[11]. Other studies have also shown that the tumor-related inflammation index is related to the tumor microenvironment and affects the body’s immune function to a certain extent. When discussing the inflammatory indicators, (in addition to the white blood cell value, neutrophil value, and C-reactive protein), other factors such as platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and lymphocyte mononuclear cell ratio (LMR), can reflect more clearly the conditions surrounding the tumor[12-14], and these are also considered to be related to the prognosis of the patient. In both the studies of gastric cancer and gastric stromal tumors, this view that inflammatory markers have an important role to play has been confirmed. With regards to the research on the prognosis of tumors, our focus was more directed to the role of the tumor microenvironment and whether the two types can be differentiated. Gastric stromal tumors are prone to be malignant, but the questions are whether they have higher inflammatory indicators and whether they are different from gastric leiomyomas; none of which has been confirmed by previous studies.

In comparison, because it has no malignant potential, the prognosis of a patient with a gastric leiomyoma is better; therefore, a gastric leiomyoma may form a better microenvironmental basis that should be reflected in the inflammation indicators. Therefore, we suspected that the identification of the two types of benign tumors could also be carried out by comparing the levels of laboratory indicators such as PLR and NLR. At the same time, combined with imaging and other methods, there may be a higher accuracy, and it could also be used for treatment. However, there is currently no relevant research showing that PLR, NLR, and other inflammatory indicators are different in the two types of tumors, and there is no research on the notion of including them in the differential diagnosis. Therefore, we conducted a retrospective study on the patients who presented with the two types of tumors in our hospital,
based on a multiple regression analysis of the influencing factors, and the total score can be calculated from a visual representation showing the probable risk of individuals with corresponding diseases[15]. In addition, it is easy to screen high-risk patients quickly and efficiently and make a timely and effective intervention [16,17]. This retrospective study aimed to explore the differences in PLR, NLR, LMR, and SII between the two types of tumors and simultaneously create a nomogram model, in order to provide a new method of differential diagnosis for clinical practice.

MATERIALS AND METHODS

This study was a retrospective cohort study approved by the Ethics Committee of the Institute of Friendship Hospital, Capital Medical University, and was conducted in accordance with good clinical practice guidelines and the Helsinki Declaration.

Patient selection

This retrospective study included 144 patients who were diagnosed with gastric stromal tumors or gastric leiomyomas from the Beijing Friendship Hospital, Capital Medical University between December, 2016 and December, 2020. There were 88 patients with gastric stromal tumors and 56 patients with gastric leiomyomas. We divided the patients into a gastric stromal tumor group and a gastric leiomyoma group according to their pathology. The two groups of patients were grouped by the postoperative pathology, and the inflammation index was calculated based on the results of the preoperative examination and the laboratory tests after the patients were admitted to the hospital. The examination results were strictly controlled to ensure that the two groups had equal examination time before surgery, as well as a thorough analysis of the patient's medication and treatment to prevent antibiotics and other drugs from affecting the patient's examination results. There were also strict admission and exclusion standards.

The eligibility criteria were as follows: (1) Age between 18 and 75 years; (2) Histologically confirmed gastric stromal tumor or gastric leiomyoma; and (3) Eastern Cooperative Oncology Group (ECOG) between 0 and 2 grades.

The exclusion criteria were as follows: (1) An unclear pathological diagnosis; (2) A history of surgery in the past six months; and (3) A history of a malignant tumor.

The definition of the inflammation index had to be supported by reference ranges, and therefore we analyzed the values of PLR, NLR, LMR, and SII. We defined PLR as the ratio of platelets to lymphocytes, NLR as the ratio of neutrophils to lymphocytes, LMR was defined as the ratio of lymphocytes to monocytes, and SII was defined as the product of neutrophils and PLR. All values were based on the results of the patient's admission and preoperative inspections, and there were no patients included with acute stress disease or antibiotic administration within half a month to ensure the reliability of the values. All patients underwent surgical treatment after completing the preoperative examination, and follow-up treatment plans were determined based on the postoperative pathology (checked by an experienced pathologist). All the material were collected following a specific procedural protocol, the size of the tumor was clearly marked for ulcers and then verified by a formal pathology report. The units of various research indicators were unified, and planning in terms of the nomogram model was carried out according to relevant research.

Statistical analyses

The primary objective of this study was the difference in the inflammation index between the two types of tumors. We recorded a patient-related data baseline to eliminate interference from the two types of patients. We hypothesized that the gastric stromal tumor and gastric leiomyoma groups had differences in related inflammatory indicators, and that could be used as the basis for a differential diagnosis. This retrospective cohort study included 88 patients in the stromal tumor group and 56 patients in the gastric leiomyoma group. We then graded according to the pathological risk, resulting in 56 people in the low-risk stromal tumor group. A subgroup analysis of gastric stromal tumor patients was performed in this group to determine whether there would be relevant numerical differences in low-risk situations. Baseline patient data were also collected. The living ability score and tumor location of the two groups were recorded and compared in the related tables. The sex and age of the patients were also included.
RESULTS

Patient characteristics
In the gastric stromal tumor group 88 were patients enrolled, and 56 patients in the gastric leiomyoma group; the relevant data of the two groups were recorded into the system for integrated analysis. Basic baseline information (sex, age, tumor location, etc.) of the two groups of patients are shown in Table 1. There were statistically significant differences between the two groups with regards to sex, age, and tumor location. In comparison, gastric leiomyomas seemed to be more common in women, young patients, and located in the gastric cardia, which is in line with our previous research.

Inflammation index
We then analyzed the inflammation indicators in the two groups. The two groups showed the following statistical differences: PLR (158.2 vs 134.3, \( P = 0.028 \)), NLR (2.35 vs 1.68, \( P = 0.000 \)), LMR (5.75 vs 10.8, \( P = 0.004 \)), and SII (546.2 vs 384.3, \( P = 0.003 \)) (Table 2). The differences in the inflammation indicators between the two groups were significant, which was in line with our conjecture before the study.

Based on multinomial logistic regression, we constructed predictive models of the GIST risk, and the results of the multivariate logistic regression analysis showed that sex, age, tumor location, and LMR were independent risk factors for the identification of the two types of tumors, and the difference was statistically significant (\( P < 0.05 \)) (Table 3).

After incorporating the risk factors selected by the above analysis into the predictive model, a predictive model for distinguishing GISTs from gastric leiomyomas was established (Figure 1). The nomogram was applied as follows: the score value corresponding to each predictive index of the score was obtained, and the sum of these score values was recorded as the total score, and the predicted probability corresponding to the total score was the risk of the GIST onset.

The calibration plot was used to explain the bias of a classifier, and the dashed line in the plot indicates the ideal model in which the predicted and actual probabilities are perfectly identical. The actual performance is indicated by a dotted line. The solid line shows the bootstrap-corrected performance. The bootstrap calibration plot (Figure 2) indicates good agreement between the nomogram and pathology results.

Subgroup analysis
In order to clarify whether there was an increase in the inflammatory response level of stromal tumors due to high risk, and whether such differences remained in existence in the relatively lower-risk stromal tumor group, we conducted a subgroup analysis and selected the low-risk group and compared that with the leiomyoma group. There were also statistical differences in some inflammation indicators (LMR 5.42 to 10.82, \( P = 0.002 \); NLR 2.17 to 1.68, \( P = 0.016 \)). We therefore inferred that LMR and NLR seemed more sensitive than PLR and SII in the subgroup analysis (Table 4).

DISCUSSION
Gastric stromal tumors and leiomyomas are both spindle cell stromal tumors, but the difference in source and malignancy should determine the type of treatment of the two types of tumors. In clinical practice, however, the two types of tumors are usually difficult to distinguish before surgical pathology is performed. For benign tumors—such as gastric leiomyomas—dynamic clinical observation is the course that should be taken, and the choice of surgery should be made with caution. Gastric leiomyoma is more likely to occur in the cardiac region, and the surgical difficulty and postoperative risk are greater in this region than in other locations. Thus, we would carefully choose the surgical option for gastric leiomyoma to avoid secondary harm to the patients. For gastric stromal tumors with malignant potential, surgical methods and surgical indications are determined according to symptoms and tumor size, and
ultrasound gastroscopy is an important tool for the differentiation of the two types of tumors; however, it remains difficult to achieve a complete differentiation between the two types of tumors in clinical practice. The guidelines state that for stromal tumors with a diameter greater than 2 cm, surgical resection is recommended as treatment because of their tendency to be malignant. However, because gastric leiomyomas originate from Cajal cells and are benign tumors, it is very important to perform accurate evaluations before surgery. In order to achieve this, a more reliable diagnosis and improved treatment standards are needed; the main purpose of this study was to determine the difference between the two types of tumors on the basis of objective clinical indicators and consider it as a type of predictive indicator. The research our center has performed confirmed our conjecture, and further research should be conducted.

Inflammation indicators reflect the balance between systemic inflammation and the body’s immune status, and compared with the white blood cell values, it tends to be more accurate. Virchow’s research linked inflammation with tumors, and also brought inflammation into tumor research, which is also the basis of this study. The values of PLR, NLR, and other inflammation-related indicators in predicting the prognosis and invasion of malignant tumors have been studied in many cases and tumors, including gastric cancer[18,19]. In terms of stromal tumors, related studies have confirmed its value in predicting prognosis. This study focused on inflammatory factors and aimed...
Inflammation-related indicators and nomogram

Table 3 Logistic regression analysis results

<table>
<thead>
<tr>
<th>Group</th>
<th>β</th>
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<td>LMR</td>
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<td>0.030</td>
<td>1.096</td>
<td>1.009-1.191</td>
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LMR: lLymphocyte mononuclear cell ratio.

Table 4 Subgroup analysis of low-risk gastrointestinal stromal tumors and gastric leiomyoma

<table>
<thead>
<tr>
<th></th>
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<th>Gastric leiomyoma (n = 56)</th>
<th>t value</th>
<th>P value</th>
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<tbody>
<tr>
<td>PLR</td>
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<td>134.3 ± 6.2</td>
<td>0.992</td>
<td>0.324</td>
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<tr>
<td>NLR</td>
<td>2.17 ± 0.17</td>
<td>1.68 ± 0.08</td>
<td>2.451</td>
<td>0.016&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>LMR</td>
<td>5.42 ± 0.32</td>
<td>10.82 ± 1.62</td>
<td>3.267</td>
<td>0.002&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>SII</td>
<td>484.5 ± 56.1</td>
<td>384.3 ± 22.1</td>
<td>1.661</td>
<td>0.101</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05.

GIST: Gastrointestinal stromal tumors; PLR: Platelet-lymphocyte ratio; NLR: Neutrophil-lymphocyte ratio; LMR: lLymphocyte mononuclear cell ratio.


to explore the difference in inflammation between the two types of tumors.

In the selected types of inflammatory factor indicators, we found differences between the two types of tumors. In this study, the inflammatory environment of gastric stromal tumors was more intricate than that of gastric leiomyomas, and the inflammatory conditions reflected by stromal tumors were more obvious. It is generally believed that tumors such as gastric stromal tumors are located in a relatively local environment and should not change the inflammatory index. However,
these differences were observed in this study. We conducted a subgroup analysis of
the stromal tumor group based on the risk grade, and compared the low-risk group
with the leiomyoma group. After that, we could still find a difference in the values of
inflammatory factors between the two groups. Based on this, we believe that gastric
stromal tumors can indeed change the inflammatory environment in which they are
located, resulting in a stronger inflammatory response in the body.

We then compared the type of inflammatory factor which had the better predictive
ability based on logistic regression analysis. We analyzed its correlation, and the
results showed that among these types of indicators, only LMR showed significance in
the regression analysis. LMR indicators may therefore be advantageous and
instructive. Compared with other indicators, LMR was more sensitive, which was a
gratifying result. We then constructed a nomogram model based on the results of
logistic regression analysis, in which we clarified the diagnostic value of sex, tumor
location, LMR, and SII. The nomogram is a visual graphical tool for predicting the
probability of individual clinical events—based on a multi-factor statistical model. It
has been widely used in various prediction models to predict the risk of disease more
accurately[20]. After the model is created (and through further improvement), it is
expected to clarify the predictor effect of the differential diagnosis for these tumors.

The relevant analysis for expanation deserves to be conducted further. How to
understand this change in inflammatory index change is a question that should be
considered. Previous studies have focused on the impact on the impact of this type of
inflammatory index on the prognosis of gastric stromal tumors. Focal lesions of gastric
stromal tumors are recognized, and the presence of immune cells in the microenvi-
ronment of gastric stromal tumors is also the basis for immunotherapy, especially the
application of imatinib[21]. Various immune cells in the tumor microenvironment,
such as tumor-associated macrophages, tumor-associated lymphocytes, and natural
killer cells exhibit characteristics related to the progression of GIST[22]. Based on this
view, gastric stromal tumors are related to changes in immunity and may influence the
body’s inflammatory response such as with gastric cancer[23]. The same results were
not found in the gastric leiomyoma group. The differences between the two types of
tumors require further research.

This study had its limitations. First, this was a retrospective study; thus, the
selection of samples and follow-up work were limited. Second, the sample size of this
study was relatively small; therefore, the results could not be generalized, and relevant
research results still need to be obtained to prove these outcomes using a large sample
size and a cohort study design. Third, we have not yet determined the reasons for such
differences, nor have we designed a corresponding scoring system based on this
feature for the next step of verification. The identification of the two types of tumors
also needs to be combined with endoscopic and imaging-related indicators, which is
an aspect that should be considered in future research. If imaging and laboratory
indicators can be combined, the prediction accuracy of the two types of tumors will
definitely be improved.
CONCLUSION

We found that there were different inflammatory states in patients with gastric leiomyomas and gastric stromal tumors. This difference could assist clinicians to distinguish between the two types of tumors before surgery in order to choose more appropriate treatments. The reason for this difference is unknown, and whether a highly sensitive scoring system can be created based on these indicators is also worth researching. Overall, we believe that the differences between the two types of tumors will aid our future clinical work; however, there is also a need to conduct further research on this aspect.

ARTICLE HIGHLIGHTS

Research background
Gastric leiomyoma and gastrointestinal stromal tumor are common tumors in the gastric mucosa. The two types of tumors are difficult to differentiate in the initial diagnosis. Inflammation-related indicators reflect the status of inflammation, which could distinguish two kinds of tumors.

Research motivation
A predictive model was constructed based on the nomogram to clarify the kind of tumors, which may help us figuring out tumor microenvironment of gastric stromal tumor. The paper will be the basis of the further research.

Research objectives
The purpose is to explore the differences in platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), lymphocyte mononuclear cell ratio (LMR), and SII between the two types of tumors, clarify the relationship and find which is the most important factor in that.

Research methods
Of 88 patients in the gastric stromal tumor group and 56 patients in the gastric leiomyoma group were enrolled into this study, and the relevant data of the two groups were entered into the system for integrated analysis. Nomogram was used to create a predictive model for that. Subgroup analysis was carried out to prove the presence of difference in low-risk stromal tumors.

Research results
The two groups were in PLR (158.2 vs 134.3, \( P = 0.028 \)), NLR (2.35 vs 1.68, \( P = 0.000 \)), LMR (5.75 vs 10.8, \( P = 0.004 \)), SII (546.2 vs 384.3, \( P = 0.003 \)) showed statistical differences. The results of the subsequent multivariate Logistic regression analysis showed that gender, age, tumor location, and LMR were independent risk factors for the identification of the two types of tumors. Nomogram model and calibration plot was constructed and subgroup analysis showed that LMR and NLR seems more sensitive than PLR and SII.

Research conclusions
It is the first time to find that inflammation-related indicators are different between gastric stromal tumors and leiomyomas, which provides us a new method to differentiate them.

Research perspectives
Further research need to be conducted to explain the reason of the the difference, and combine other examinations, such as computed tomography, to create an appropriate model for that.

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Tan Y, Garcia-Buitrago MT, Trent JC, Rosenberg AE. The immune system and gastrointestinal

Retrospective Study

Relationship between Ki-67 and CD44 expression and microvascular formation in gastric stromal tumor tissues

Bing Ma, Xiao-Tian Huang, Gui-Jun Zou, Wen-Yu Hou, Xiao-Hui Du

ORCID number: Bing Ma 0000-0002-0683-1396; Xiao-Tian Huang 0000-0002-5149-4608; Gui-Jun Zou 0000-0002-2682-0587; Wen-Yu Hou 0000-0002-0639-7614; Xiao-Hui Du 0000-0001-7083-2046.

Author contributions: Ma B and Du XH performed the research; Huang XT contributed new reagents and analytic tools; Zou GJ and Hou WY analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the PLA General Hospital Institutional Review Board (Approval No. 20210321).

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

Conflict-of-interest statement: None conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

Specialty type: Gastroenterology and Hepatology

Provenance and peer review: Unsolicited article; Externally peer

Abstract

BACKGROUND
A gastric stromal tumor (GST) is a mesenchymal tumor that occurs in the gastrointestinal tract; its biological characteristics are highly complex. Clinically, the severity of a GST is often evaluated by factors such as risk classification, tumor size, and mitotic figures. However, these indicators are not very accurate. Even patients classified as low risk are also at risk of metastasis and recurrence. Therefore, more accurate and objective clinical biological behavior evaluations are urgently needed.

AIM
To determine the relationship between Ki-67 and CD44 expression in GSTs and microvessel formation and prognosis.

METHODS
Eighty-six GST tissue specimens from our hospital were selected for this study. The immunohistochemical staining technique was used to detect Ki-67, CD44, and microvessel density (MVD) in the collected samples to analyze the different risk grades and mitotic figures. In addition, this approach was used to determine the differences in the expression of Ki-67 and CD44 in GST tissues with varying lesion diameters.

RESULTS
In GSTs with positive expression of the Ki-67 protein, the proportions of patients with medium-to-high risk and more than five mitotic counts were 24.07% and 38.89%, respectively. In GSTs with positive expression of the CD44 protein, the proportions of patients with medium-to-high risk and more than five mitotic counts were 23.73% and 38.98%, respectively. In GSTs with negative expression of the Ki-67 protein, these values were relatively high (3.70% and 11.11%, respectively). The MVD in GSTs with positive and negative expression of the CD44 protein was 15.92 ± 2.94 and 13.86 ± 2.98/Hp, respectively; the difference
between the two groups was significant ($P < 0.05$).

**CONCLUSION**

Ki-67 and CD44 expression in GSTs is correlated with the grade of tumor risk and mitotic figures. CD44 expression is correlated with microvessel formation in tumor tissues.

**Key Words:** Gastric stromal tumor; Ki-67; CD44; Expression; Microvascular formation; Formation of microvessels

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**Core Tip:** Microvascular plays a key role in the occurrence and development of gastric stromal tumor. Through this study, we reveal its role in tumor metastasis and invasion, and provide a basis for predicting the clinical prognosis of patients.

**INTRODUCTION**

A gastric stromal tumor (GST) is a type of gastrointestinal tumor. In recent years, the incidence of GSTs has been continuously increasing. Owing to the instability of their biological behavior, it is difficult to diagnose GSTs\(^1,2\). Immunohistochemical markers can help predict the prognosis and determine the risk of GSTs. CD44 has recently been found to be an important indicator, showing specificity in many tumors. However, its expression characteristics in GSTs remain controversial\(^3\). Ki-67, meanwhile, is involved in the process of cell proliferation and is highly expressed in breast cancer and neuroendocrine carcinoma\(^4\). The role of neovascularization in the biological process of tumorigenesis cannot be ignored. Many studies have shown that GSTs contain large amounts of pro-angiogenic factors\(^5\), but few studies have addressed the relationship between GSTs and microvessel density (MVD). The microvasculature plays a key role in the occurrence and development of tumors. It can also induce and mediate the biological processes underlying tumorigenesis, such as participating in the processes of metastasis and tumor invasion. MVD is thus a representative quantitative indicator reflecting tumor vascular growth. It is relevant to tumor nutrition and oxygen supply\(^6\). This study explored the relationship between Ki-67 and CD44 expression in GST tissues and microangiogenesis.

**MATERIALS AND METHODS**

**Tissue specimens**

Tissue specimens of 86 cases of GSTs that were surgically resected in our hospital from April 2016 to February 2019 were selected for this study. The inclusion criteria were as follows: (1) Updates and interpretations of the National Comprehensive Cancer Network Clinical Practice Guidelines (2019 6th version) on GSTs\(^7\); (2) Patients were examined prior to their operation via preoperative computer tomography and gastroscopy biopsies; and (3) Patients had no history of radiotherapy, chemotherapy, or immunological treatment before surgery. This study was approved by the Medical Ethics Committee, and all baseline data of patients were complete. The criteria for exclusion were as follows: (1) GSTs were accompanied by other types of tumor diseases; (2) Data were missing and unable to be included for statistical analysis; (3) Patients had local recurrence; or (4) Pathological examinations were lacking.
Eighty-six GST patients aged 41 to 79 years, with an average of 62.0 ± 6.8 years, were selected. There were 35 males and 51 females. The lesion sites were as follows: gastric antrum (12 cases), gastric body (19 cases), and gastric fundus (55 cases). Fifty-six cases had tumors with a diameter larger than 2.0 cm; 30 cases had a diameter equal to or less than 2.0 cm. There were 60 cases with mitotic counts equal to or less than five; 26 cases had more than five mitotic counts. The risk classifications were as follows: very low risk (32 cases), low risk (39 cases), and medium high risk (15 cases).

**Immunohistochemical test**

Paraffin sections (thickness of 4 μm) were prepared in a conventional manner. The sections were de-waxed with xylene and gradient alcohol (100%, 100%, 95%, 95%, 80%, and 70%) to water, stepwise. Distilled water was used to rinse the sections twice (3 min each time), and phosphate buffered saline (PBS) was used to rinse the sections three times (3 min each time). The samples were then rinsed with tap water and soaked in distilled water for storage. Subsequently, the sections were placed in 10 mmol of LPH6.0 citrate buffer for antigen repair. Next, the sections were rinsed in a gentle manner under running water to bring them to room temperature. Primary antibodies were added to the tissues, which were then incubated for 16 h on a shaking table at 4 °C. After incubation, the tissues were rinsed three times with PBS (5 min each time). The primary antibodies were not added to the negative group, and only PBS was added. Then, the secondary antibodies were added and incubated for 30 min before rinsing, according to the aforementioned method. One drop of DAB was then added to each section to aid in color development, following which the sections were incubated at room temperature for 5 min. The sections were then re-stained with hematoxylin and immersed in 1% hydrochloric acid alcohol for 30 s, 1% ammonia alcohol for 45 s, and alcohol for 1 min. They were then transparentized with xylene and sealed with neutral gum.

**Determination of immunohistochemistry results**

Positive staining of Ki-67 and CD44 proteins in the nucleus or cytoplasm is shown in

### Table 1 Relationship between the expression of different Ki-67 proteins and characteristics of gastric stromal tumors, n (%)

<table>
<thead>
<tr>
<th>Index</th>
<th>Ki-67 Protein positive (n = 54)</th>
<th>Ki-67 Protein negative (n = 32)</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>29 (53.70)</td>
<td>21 (65.63)</td>
<td>1.173</td>
<td>0.279</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>25 (46.30)</td>
<td>11 (34.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.844</td>
<td>0.358</td>
</tr>
<tr>
<td>Male</td>
<td>24 (44.44)</td>
<td>11 (34.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30 (55.56)</td>
<td>21 (65.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric antrum</td>
<td>7 (12.96)</td>
<td>5 (15.63)</td>
<td>1.250</td>
<td>0.535</td>
</tr>
<tr>
<td>Body of stomach</td>
<td>14 (25.93)</td>
<td>5 (15.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base of stomach</td>
<td>33 (61.11)</td>
<td>22 (68.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk classification</td>
<td></td>
<td></td>
<td>7.380</td>
<td>0.025</td>
</tr>
<tr>
<td>Very low risk</td>
<td>15 (27.78)</td>
<td>17 (53.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>26 (48.15)</td>
<td>13 (40.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium and high risk</td>
<td>13 (24.07)</td>
<td>2 (6.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitosis</td>
<td></td>
<td></td>
<td>5.156</td>
<td>0.023</td>
</tr>
<tr>
<td>≤ 5</td>
<td>33 (61.11)</td>
<td>27 (84.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5</td>
<td>21 (38.89)</td>
<td>5 (15.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion diameter (cm)</td>
<td></td>
<td></td>
<td>1.764</td>
<td>0.184</td>
</tr>
<tr>
<td>&gt; 2.0 cm</td>
<td>38 (70.37)</td>
<td>18 (56.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2.0 cm</td>
<td>16 (29.63)</td>
<td>14 (43.75)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
yellow, brownish yellow, or brown: (1) According to the degree of staining, the results were categorized as follows: non-staining (0 points), only pale yellow staining (1 point), brownish yellow staining (2 points), and brown or black staining (3 points); and (2) According to the proportion of stained cells, the results were categorized as follows: equal to or less than 10% (one point), from 11% to 50% (two points), from 51% to 75% (three points), and more than 75% (four points). Products of staining degree and scores of positive cells that were less than three points were considered negative, whereas products that were equal to or greater than three points were considered positive.

**MVD detection and counting method**

The segments were reviewed by two experienced pathologists with a double-blind approach. First, high MVD regions in the tissues were identified using a low-power microscope. A high-power lens with a 200-fold microscope was then used to identify individual vascular endothelial cells with brown or tan staining. The numbers of stained microvessels were counted with a microscope at five different fold magnifications, and the average value was considered the MVD (microvessels exhibit significant differences in MVD from adjacent microvessels, tumor cells, or connective tissue components).

**Statistical analysis**

Statistical analysis was performed using SPSS 21.0 software. MVD in tissues with different Ki-67 and CD44 protein expression levels is presented as mean ± SD. The two groups were compared using independent sample t-tests. The positive expression rates of Ki-67 and CD44 proteins were evaluated using a χ² test. The logistic regression model was used for multi-factor analysis. P < 0.05 was considered to represent a significant difference.

### Table 2 Relationship between the expression of different CD44 proteins and characteristics of gastric stromal tumors, n (%)

<table>
<thead>
<tr>
<th>Index</th>
<th>CD44 protein positive (n = 59)</th>
<th>CD44 protein negative (n = 27)</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td>1.176</td>
<td>0.278</td>
</tr>
<tr>
<td>≥ 60</td>
<td>32 (54.24)</td>
<td>18 (66.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>27 (45.76)</td>
<td>9 (33.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.884</td>
<td>0.347</td>
</tr>
<tr>
<td>Male</td>
<td>26 (44.07)</td>
<td>9 (33.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33 (55.93)</td>
<td>18 (66.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion site</td>
<td></td>
<td></td>
<td>1.283</td>
<td>0.256</td>
</tr>
<tr>
<td>Gastric antrum</td>
<td>7 (11.86)</td>
<td>5 (18.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body of stomach</td>
<td>12 (20.34)</td>
<td>7 (25.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base of stomach</td>
<td>40 (67.80)</td>
<td>15 (55.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk classification</td>
<td></td>
<td></td>
<td>6.534</td>
<td>0.038</td>
</tr>
<tr>
<td>Very low risk</td>
<td>18 (30.51)</td>
<td>14 (51.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>27 (45.76)</td>
<td>12 (44.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium and high risk</td>
<td>14 (23.73)</td>
<td>1 (3.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitosis</td>
<td></td>
<td></td>
<td>6.822</td>
<td>0.009</td>
</tr>
<tr>
<td>≤ 5</td>
<td>36 (61.02)</td>
<td>24 (88.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5</td>
<td>23 (38.98)</td>
<td>3 (11.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion diameter (cm)</td>
<td></td>
<td></td>
<td>1.584</td>
<td>0.208</td>
</tr>
<tr>
<td>&gt; 2.0 cm</td>
<td>41 (69.49)</td>
<td>15 (55.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2.0 cm</td>
<td>18 (30.51)</td>
<td>12 (44.44)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RESULTS

Relationship between different Ki-67 protein expression levels and risk grade, mitotic counts, and GST lesion diameters

The percentages of patients with tumor risk grade (medium-to-high risk) and mitotic counts (> 5) in GSTs with positive expression of the Ki-67 protein were 24.07% and 38.89%, respectively. These values were higher than those of patients with negative expression of the Ki-67 protein (6.25% and 15.63%, respectively); the difference was significant ($P < 0.05$). There were no significant differences between the positive expression rates of the Ki-67 protein in GST tissues and different lesion diameters, ages, sexes, or lesion locations ($P > 0.05$; Table 1 and Figure 1).

Relationship between different CD44 protein expression levels and risk grade, mitotic counts, and GST lesion diameters

Patients classified as medium-to-high risk with CD44 protein-positive expression in GST and patients with more than five mitotic counts accounted for 23.73% and 38.98%, respectively. These values were higher than those of Ki-67-negative patients (3.70% and 11.11%, respectively); the difference was significant ($P < 0.05$). There were no significant differences between the positive expression rates of the CD44 protein in GST tissues and different lesion diameters, ages, sexes, or lesion locations ($P > 0.05$; Table 2 and Figure 2).

Comparison of MVD in GST tissues with different Ki-67 and CD44 protein expression levels

There was no significant difference in MVD between GST tissues with positive and negative expression of the Ki-67 protein ($P > 0.05$; Table 3). There was, however, a significant difference in MVD between GST tissues with positive and negative expression of the CD44 protein ($P < 0.05$; Table 3).

DISCUSSION

CD44, which is a transmembrane protein belonging to the cell adhesion molecule family, theoretically plays a certain role in tumor progression and metastasis[8,9]. A reduction in the expression level of CD44 would lead to poor adhesion between cells, making tumor cells more likely to shed and metastasize. However, studies have shown that the CD44 protein might play diverse and complex roles in the metastasis of different types of malignancies[10,11]. In this study, an immunohistochemical technique was used to detect the expression of CD44 in GSTs. It was found that the expression of CD44 was related to the risk grade and mitotic figures of GSTs, thus indicating that mitotic figures and the primary site could be independent prognostic factors[10-12]. The results of this study showed that high pathological risk grades, increased mitotic figures, and positive expression of the CD44 protein in patients with GSTs were independent risk factors for poor prognosis. CD44 could be involved in the angiogenic process in GSTs and mediate their recurrence or metastasis. Nonetheless, combining CD44 with tumor diameter and mitotic figures to more accurately evaluate and grade the risk of GSTs remains a challenge; future studies with larger sample sizes and longer follow-up times should be conducted to this effect.

Reportedly, high MVD in GSTs is related to risk classification, tumor size, and mitotic counts. MVD is an independent factor that affects the prognosis in patients[13-15]. The results of this study showed that there was a significant difference in MVD between tissues that were positive and negative for the CD44 protein. CD44 can promote tumor proliferation and further promote the generation of new blood vessels in tumor issues. However, new vascular basement membranes in tumors are not mature; their vascular walls are not closely arranged and are relatively loose. Thus, tumor cells can easily pass through these walls and enter the blood vessels, where they can diffuse. When the tumor spreads further, large numbers of blood vessels are further generated and MVD increases significantly. This, in turn, increases the opportunity for tumor cells to directly contact blood cells, thus promoting the infiltration and metastasis of the tumor cells. The increased expression level of CD44 provides sufficient blood supply and nutrition for angiogenesis and tumor cell proliferation. This study showed that the generation of microvessels in GSTs is relevant to the expression of CD44.
Ma B et al. Microvascular formation in GST tissues

Table 3 Comparison of microvessel density in gastric stromal tumor tissues with different expression of Ki-67 and CD 44 protein (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>MVD (/Hp)</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67 expression</td>
<td></td>
<td></td>
<td>0.889</td>
<td>0.377</td>
</tr>
<tr>
<td>Positive</td>
<td>54</td>
<td>15.41 ± 3.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>32</td>
<td>14.82 ± 2.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD44 expression</td>
<td></td>
<td></td>
<td>3.003</td>
<td>0.004</td>
</tr>
<tr>
<td>Positive</td>
<td>59</td>
<td>15.92 ± 2.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>27</td>
<td>13.86 ± 2.98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MVD: Microvessel density.

Figure 1 Ki-67 protein expression in gastric stromal tumor tissue. A: Positive expression; B: Negative expression (×200).

Figure 2 CD44 protein expression in gastric stromal tumor tissue. A: Positive expression; B: Negative expression (×200).

Some studies[9,16,17] have argued that increased Ki-67 expression level indicates that the tumor cells are growing rapidly, as Ki-67 can reflect the growth state of tumor cells. The results of the present study showed that there was a correlation between Ki-67 and the mitotic count. The mitotic count only reflects the M phase of cell proliferation, whereas Ki-67 is expressed in the G1, S, G2, and M phases of cell proliferation [18,19]. Currently, the standard of Ki-67 expression in GSTs is unclear. This is likely because Ki-67 expression is only considered a marker of tumor proliferation from quantitative to qualitative change. In addition, the present study found that Ki-67 is more reliable than tumor size in predicting tumor risk classification and different mitotic counts.

We found that there was no significant difference between the level of MVD in GST tissues and negative Ki-67 protein expression groups. There was no correlation between the formation of microvessels in GST tissues and the expression of the Ki-67.
protein, but this lack of correlation might have been due to the limitation of the small sample size. Although Ki-67 expression was found to be irrelevant to MVD in GST tissues, it might be a candidate indicator for the prognostic evaluation of GSTs because of its association with tumor risk grade and mitotic counts.

CD44 expression provides a certain clinical reference value for the prognoses of GSTs. Reducing MVD and inhibiting CD44 expression could suppress angiogenesis in GSTs and provide new targets for their treatment. However, the specific mechanisms need to be studied further [20].

To date, few reports have examined the relationship between Ki-67 and CD44 protein expression and the GST risk grade, as well as the changes in mitotic counts. Therefore, it is of certain significance to elucidate the mechanisms by which Ki-67 and CD44 play a role in tumorigenesis. Although there have been various speculations regarding the mechanisms of the two genes, the synergistic effects and mechanisms thereof, as well as their expression products, in the occurrence and development of GSTs remain unclear.

CONCLUSION

In summary, the expression of Ki-67 and CD44 in GSTs has certain relationships with the tumor risk grade and mitotic changes. The expression of CD44 is related to microvessel formation in tumor tissues and the prognosis in patients with GSTs.

ARTICLE HIGHLIGHTS

Research background
The incidence of gastric stromal tumors (GSTs) is increasing. The severity of a GST is often evaluated by factors such as risk classification, tumor size, and mitotic figures. However, these indicators are not very accurate.

Research motivation
Few studies have addressed the relationship between GSTs and microvessel density.

Research objectives
In this study, the authors aimed to explore the relationship between Ki-67 and CD44 expression in GST tissues and microangiogenesis.

Research methods
Tissue specimens of 86 cases of GSTs were selected for this study. All cases met the inclusion and exclusion criteria.

Research results
High pathological risk grades, increased mitotic figures, and positive expression of the CD44 protein in patients with GSTs were independent risk factors for poor prognosis.

Research conclusions
The expression of Ki-67 and CD44 in GSTs has certain relationships with the tumor risk grade and mitotic changes.

Research perspectives
A deeper study with a larger sample size is needed to confirm this finding.

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Retrospective Study

Modified surgical method of supra- and infratentorial epidural hematoma and the related anatomical study of the squamous part of the occipital bone

Rui-Chun Li, Shi-Wen Guo, Chen Liang

BACKGROUND

Supra- and infratentorial acute epidural hematoma (SIEDH) is a common posterior cranial fossa epidural hematoma located at the inner surface of the squamous part of the occipital bone (SOB). Traditionally, surgical treatment of the SIEDH requires a combined supra-infratentorial craniotomy.

AIM

To analyze the morphological characteristics of the SOB and introduce a single supratentorial craniotomy for SIEDH.

METHODS

Skull computed tomography (CT) scan data from 32 adult patients were collected from January 1, 2019 to January 31, 2020. On the median sagittal plane of the CT scan, the angle of the SOB (ASOB) was defined by two lines: Line A was defined from the lambdoid suture (LambS) to the external occipital protuberance (EOP), while line B was defined from the EOP to the posterior edge of the foramen magnum (poFM). The operative angle for the SIEDH (OAS) from the supra- to infratentorial epidural space was determined by two lines: The first line passes from the midpoint between the EOP and the LambS to the poFM, while the second line passes from the EOP to the poFM. The ASOB and OAS were measured and analyzed.

RESULTS

Based on the anatomical study, a single supratentorial craniotomy was performed in 8 patients with SIEDH. The procedure and the results of the modified surgical method were demonstrated in detail. For males, the ASOB was 118.4 ± 4.7 and the OAS was 15.1 ± 1.8; for females, the ASOB was 130.4 ± 5.1 and the OAS was 12.8 ± 2.0. There were significant differences between males and females both in ASOB...
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Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

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INTRODUCTION

Supra- and infratentorial acute epidural hematoma (SIEDH) is a common posterior cranial fossa epidural hematoma located at the inner surface of the squamous part of the occipital bone (SOB)[1-3]. Most SIEDHs are caused by direct violence to the occipital bone due to traffic accidents and falls[4-6]. The traditional surgical method requires a tedious combined supra-infratentorial craniotomy to evacuate the SIEDH[2, 7, 8]. However, the SOB does not present as a single straight plane, but bends at an angle around the external occipital protuberance (EOP) and the superior nuchal lines, which divide the SOB into the supra- and infratentorial areas, respectively[9]. As the angle of the SOB (ASOB) is less than 180, there is an operative angle for the SIEDH negatively correlated with the angle of the SOB. These morphological characteristics of the SOB make it possible to treat SIEDH with a single supratentorial craniotomy. Based on the above findings, we used a single supratentorial craniotomy to treat SIEDH, and achieved satisfactory results.

In this study, the ASOB and the OAS were analyzed quantitatively. An illustrative case example is presented to demonstrate the technique nuances of the modified surgical method.

MATERIALS AND METHODS

ASOB

The SOB is located above the posterior edge of the foramen magnum and articulates with the parietal bone at the lambdoid suture (LambS). The EOP, with the superior nuchal lines radiated laterally from it, is situated at the central part of the external surface of the SOB and divides the SOB into superior and inferior parts. The two parts form an angle with the EOP at the vertex (schematic representation in Figure 1).

On the median sagittal plane of the computed tomography (CT) scan, the ASOB was defined by two lines: One is from the EOP to the LambS, and the other is from the EOP to the posterior edge of the foramen magnum (poFM) (Figure 2A).

and OAS. The smaller the ASOB was, the larger the OAS was. The bone flaps in 8 patients were designed above the transverse sinus intraoperatively, and the SIEDH was completely removed without suboccipital craniotomy. The SOB does not present as a single straight plane but bends at an angle around the EOP and the superior nuchal lines. The OAS was negatively correlated with the ASOB.

CONCLUSION

The single supratentorial craniotomy for SIEDH is reliable and effective.

Key Words: Epidural hematoma; External occipital protuberance; Occipital bone; Transverse sinus; Supra- and infratentorial acute epidural hematoma; Modified surgical method

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Core Tip: Traditionally, surgical treatment of a supra- and infratentorial acute epidural hematoma (SIEDH) requires a combined supra-infratentorial craniotomy. We analyzed the morphological characteristics of the squamous part of the occipital bone (SOB) and found that the operative angle for the SIEDH was negatively correlated with the angle of the SOB. These morphological characteristics of the SOB make it possible to treat SIEDH with a single supratentorial craniotomy. Based on the above findings, we used a single supratentorial craniotomy to treat SIEDH, and achieved satisfactory results.

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Li RC et al. Modified surgical method of the SIEDH

Figure 1 Schematic representation of the angle of the squamous part of the occipital bone on the outer surface of the occipital bone. The vertex of the angle of the squamous part of the occipital bone was located at the external occipital protuberance (EOP), while the two edges of the angle were demonstrated by two yellow arrow lines directed from the EOP to the lambdoid suture and the posterior edge of the foramen magnum (red star) in the median sagittal plane, respectively. OMS: Occipitomastoid suture; PMS: Parietomastoid suture; LambS: Lambdoid suture; EOP: External occipital protuberance.

Figure 2 Schematic representation of the angle of the squamous part of the occipital bone and the operative angle for the supra- and infratentorial epidural hematoma on the median sagittal plane of the computed tomography scan. A: The angle of the squamous part of the occipital bone, symbolized as θ, was defined between two orange arrow lines from the external occipital protuberance (EOP) to the lambdoid suture (LambS) and to the posterior edge of the foramen magnum (poFM), respectively. The EOP is located at the level of the transverse sinus; B: The "S" denotes the midpoint between the EOP and the LambS; the "I" denotes the point of the poFM. The α represents the operative angle for the supra- and infratentorial epidural hematoma. As the θ is less than 180, the angle α is not equal to zero. EOP: External occipital protuberance; LambS: Lambdoid suture; poFM: Posterior edge of the foramen magnum.

OAS
On the median sagittal plane of the CT scan, an angle was defined to analyze the OAS quantitatively. The OAS was determined by two intersecting lines with the vertex located at the poFM. The first line passes from the midpoint between the EOP and the LambS to the poFM, while the second line passes from the EOP to the poFM (Figure 2B). Theoretically, the OAS can represent the surgical freedom for clearance of the SIEDH from the supra- to infratentorial epidural space by a single supratentorial craniotomy. Mathematically, the greater the OAS is, the bigger the operative corridor is.

Radiological data
The skull CT scans of 32 adult patients (16 males and 16 females, aged from 18 to 65 years) were collected in the Neurosurgical Department of Xi’an Jiaotong University from January 1, 2019 to January 31, 2020. These patients included 22 cases of intracranial aneurysms and 8 cases of acoustic schwannomas. The ASOB and OAS were measured on the median sagittal plane of the CT scans and the data were analyzed statistically.
**Patients with SIEDH**

A total of 8 patients with SIEDH were surgically treated from July 1, 2017 to March 31, 2020. These patients consisted of 6 males and 2 females, aged from 23 to 49 years (mean 32.5 ± 10.5 years). Seven cases were admitted following traffic accidents and 1 case following a fall injury. Three of these patients had occipital and frontal lobe contusion and laceration. The admission Glasgow Coma Score (GCS) was 9 points in 3 cases, 10 points in 4 cases and 11 points in 1 case (median 10 points).

**Modification of the surgical method**

After general anesthesia, the patients were positioned laterally with the head fixed by a Mayfield head frame (Integra LifeSciences Corporation, Cincinnati, OH, United States). According to the location of the hematoma, a unilateral occipital skin flap was incised and the boundary of the bone flap was defined by 4 Lines: The midline, the lateral edge of the hematoma, the upper edge of the hematoma and the lower margin of the transverse sinus (Figure 3). Four bony holes were drilled using the Medtronic high-speed drill (Medtronic, Minneapolis, MN, United States) at the corners of the bone flap, and a supratentorial craniotomy was completed. Subsequently, the supratentorial part of the SIEDH was gradually removed by suction and forceps. When the dura mater was exposed, the bleeding arteries on the dura were immediately electrocoagulated. In the transverse sinus region, the hematoma was carefully evacuated and a gelatin sponge was used to stop the bleeding from the sinus. The inferior part of the SIEDH was then explored and evacuated. Finally, the dura mater was carefully suspended at the edge of the craniectomy and the bone flap was fixed in situ.

**Statistical analysis**

The Shapiro-Wilk test was used to analyze the normality of the data, and Levene’s test was used to analyze the homogeneity of variance. The t-test was used for comparisons between the two groups when the data were in accordance with normal distribution and homogeneity of variance, otherwise the Rank sum test was used. A two-tailed \( P < 0.05 \) indicated statistical significance. All statistics were performed with R version 4.0.2.

**RESULTS**

**Statistical analysis of the ASOB and OAS**

The ASOB of male patients was smaller than that of female patients (118.4 ± 4.7 vs 130.4 ± 5.1), while the OAS of males was greater than that of females (15.1 ± 1.8 vs 12.8 ± 2.0). These data are shown in Table 1. These results indicated that the smaller the ASOB was, the greater the OAS was.

**Clinical presentation**

A skull CT examination was performed within 24 h postoperatively. The SIEDH was totally removed in all 8 cases. The postoperative GCS scores were 10 in 4 cases, 11 in 2 cases, 12 in 1 case and 13 in 1 case 72 h after surgery. The median score was 10.5, which was significantly higher than that before surgery (Table 2). Postoperatively, one patient developed pneumonia which was cured by antibiotic treatment within 2 wk. Intracranial infection, subcutaneous effusion and cerebrospinal fluid leakage were not observed.

**Illustrative case**

A 29-year-old man was admitted to hospital 3 h after a traffic accident. The admission GCS score was 10. The CT examination revealed a left SIEDH and scalp hematoma (Figure 4A). Surgical treatment was carried out according to the method described above. Intraoperatively, a linear fracture of the occipital bone extended from the LambS to the mastoid (Figure 3B), which was the source of the epidural hematoma. The hematoma covering the transverse sinus area separated the dura from the inner surface of the skull, which created a surgical corridor from supratentorial to infratentorial (Figure 3C). The hematoma was completely cleared, which was confirmed by a postoperative CT scan (Figures 3D and 4B). The bone flap was perfectly reset and fixed without any obvious bone defects (Figure 4B).
Table 1 Statistical analysis of the angle of the squamous part of the occipital bone and the operative angle for the supra- and infratentorial epidural hematoma between male and female

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 16), mean ± SD (min, max)</th>
<th>Female (n = 16), mean ± SD (min, max)</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASOB</td>
<td>118.4 ± 4.7 (108.3, 126.9)</td>
<td>130.4 ± 5.1 (123.2, 139.1)</td>
<td>6.946</td>
<td>&lt; 0.001³</td>
</tr>
<tr>
<td>OAS</td>
<td>15.1 ± 1.8 (12.6, 18.5)</td>
<td>12.8 ± 2.0 (8.6, 16.4)</td>
<td>3.301</td>
<td>0.003³</td>
</tr>
</tbody>
</table>

*P < 0.05. ASOB: Angle of the squamous part of the occipital bone; OAS: Operative angle for the SIEDH.

Table 2 Comparison of Glasgow coma score before and after operation

<table>
<thead>
<tr>
<th></th>
<th>Preoperation</th>
<th>Postoperation</th>
<th>Rank sum test</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td>9, 9, 9, 10, 10, 10, 11</td>
<td>10, 10, 10, 11, 11, 12, 13</td>
<td>P = 0.037⁷</td>
</tr>
</tbody>
</table>

*P < 0.05. GCS: Glasgow coma score.

**DISCUSSION**

The SIEDH, which traverses the transverse sinus from the supratentorial to inferior tentorial, represents 11%-64% of all posterior fossa epidural hematomas[2,3,6]. Due to potential severe brain edema due to compression on the transverse sinus by the hematoma, some scholars have suggested aggressive surgical treatment even if the hematoma volume is small[6-8]. Traditionally, a combined supra-inferior craniotomy was recommended. The supratentorial bone flap was reset at the end of surgery, while the infratentorial bone, in the suboccipital area, was removed. The purpose of the traditional method was to maximize exposure of the hematoma and thoroughly remove it[8-10]. However, the combined supra-inferior craniotomy has the following disadvantages: Firstly, it requires the cutting of multi-layer muscles in the suboccipital area, which can be time-consuming and increase blood loss; secondly, a suboccipital craniotomy is often accompanied by a subsequent large bone defect[11]. To avoid a large bone defect in the suboccipital area, Wang and Guoping[7] recommended a single supratentorial craniotomy to remove the SIEDH. Their research showed that this technique led to efficient total evacuation of the SIEDH.

Therefore, based on the anatomical characteristics of the SOB, this study theoretically demonstrated the feasibility of single supratentorial craniotomy in the treatment of SIEDH.

According to Rhoton's research, the occipital bone is divided into a SOB part located above and behind the foramen magnum, a basal part situated in front of the foramen magnum, and paired condylar parts located lateral to the foramen magnum[9,12]. The SOB extends from the foramen magnum inferiorly to the LambS superiorly. The EOP and the superior nuchal lines divide the SOB into superior and inferior parts which locate up and down to the transverse sinus, respectively. The inferior part of the SOB is also called the suboccipital area with a rough outer surface which serves as the site of attachment of numerous muscles including the trapezius, sternocleidomastoid, splenius capitis and semispinalis muscles, etc.[9].

In this study, we found that the superior and inferior parts of the SOB were not located in one plane but were connected at an intersection angle (ASOB). The ASOB in males was smaller than that in females (118.4 ± 4.7 vs 130.4 ± 5.1). As the ASOB was less than 180 in both males and females, when elevating the dura, there was an operative corridor for evacuation of the SIEDH from the supratentorial to infratentorial epidural space in a single supratentorial craniotomy. The OAS was used to analyze this operative corridor quantitatively and the study revealed that the OAS in males was greater than that in females (15.1 ± 1.8 vs 12.8 ± 2.0). These results indicated that the smaller the ASOB is, the greater the OAS is. These anatomical morphological characteristics are extremely important for modification of the surgical method.

Intraoperatively, we performed a single craniotomy above the transverse sinus. After the supratentorial part of the SIEDH had been cleared, the dura of the transverse sinus was often found to be peeled off from the inner surface of the skull. In the 8 cases
Figure 3 Modified surgical method of supra- and infratentorial epidural hematoma. A: The white arrow points to the surface projection of the transverse sinus. The skin flap was close to the midline medially, reaching the lateral edge of the hematoma laterally, up to the upper edge of the hematoma superiorly, and about 1 cm below the transverse sinus inferiorly (yellow triangle). The lower edge of the bone flap was located at the upper edge of the transverse sinus. The orange arrow indicates the midline of the head; B: After elevating the skin flap, a linear fracture of the occipital bone was found (white arrow); C: Subsequently the bone flap was opened to expose the supra- and infratentorial epidural hematoma (SIEDH). The white arrow shows the lower edge of the bone window across the superior edge of the transverse sinus. The yellow arrow demonstrated that the SIEDH can be cleared from above to below the transverse sinus; D: After the SIEDH was completely removed, the dura was tightly suspended on the periosteum.

included in this study, all the infratentorial part of the SIEDHs were explored and removed completely. This modified surgical method of the single supratentorial craniotomy omitted the tedious steps of infratentorial craniotomy and its complications were also avoided.

However, the number of cases in this study was relatively small, and there were no cases with transection or laceration of the transverse sinus. In such situations, the combination of supra-inferior tentorial craniotomy should be performed to control the abundant bleeding through a greater range of exposure[13].

CONCLUSION

The SOB does not present as a single straight plane but bends at an angle around the EOP and the superior nuchal lines, and the smaller the ASOB was, the larger the OAS was. These morphological characteristics of the SOB make it possible to evacuate the SIEDH from the supra- to infratentorial epidural space by a single supratentorial craniotomy.
Figure 4 A pre- and postoperative computed tomography scan of a 29-year-old man after a traffic accident. A: The preoperative computed tomography (CT) scan showed the left supra- and infratentorial acute epidural hematoma (SIEDH) across the transverse sinus and the local occipital scalp hematoma; B: 24 h after surgery, the head CT showed that the SIEDH was completely cleared and the bone flap was perfectly fixed in situ.

ARTICLE HIGHLIGHTS

Research background
Traditional surgical treatment of the supra- and infratentorial acute epidural hematoma (SIEDH) requires a combined supra-infratentorial craniotomy.

Research motivation
To modify the surgery method according to the results of anatomical research.

Research objectives
To analyze the morphological characteristics of the squamous part of the occipital bone (SOB) and introduce a single supratentorial craniotomy for SIEDH.

Research methods
Skull computed tomography scan data from 32 adult patients were collected. The angle of the SOB (ASOB) and the operative angle for the SIEDH (OAS) were measured and analyzed.

Research results
For males, the ASOB was 118.4 ± 4.7 and the OAS was 15.1 ± 1.8; for females, the ASOB was 130.4 ± 5.1 and the OAS was 12.8 ± 2.0. The smaller the ASOB was, the larger the OAS was. Based on the anatomical study, a single supratentorial craniotomy was performed in 8 patients with SIEDH, and the SIEDH was completely removed.

Research conclusions
The single supratentorial craniotomy for SIEDH is reliable and effective.

Research perspectives
It is hoped that the results of this study can improve the efficiency of surgical treatment of SIEDH.

ACKNOWLEDGEMENTS
We thank Professor Wang Y, the Department of Anatomy of Medical College of Xi’an Jiaotong University, for providing radiological data for this study.

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Combined molybdenum target X-ray and magnetic resonance imaging examinations improve breast cancer diagnostic efficacy

Wen-Quan Gu, Sun-Mei Cai, Wei-Dong Liu, Qi Zhang, Ying Shi, Li-Juan Du

Abstract

BACKGROUND

Early-stage breast cancer patients often lack specific clinical manifestations, making diagnosis difficult. Molybdenum target X-ray and magnetic resonance imaging (MRI) examinations both have their own advantages. Thus, a combined examination methodology may improve early breast cancer diagnoses.

AIM

To explore the combined diagnostic efficacy of molybdenum target X-ray and MRI examinations in breast cancer.

METHODS

Patients diagnosed with breast cancer at our hospital from March 2019 to April 2021 were recruited, as were the same number of patients during the same period with benign breast tumors. Both groups underwent molybdenum target X-ray and MRI examinations, and diagnoses were given based on each exam. The single (i.e., X-ray or MRI) and combined (i.e., using both methods) diagnoses were counted, and the MRI-related examination parameters (e.g., T-wave peak, peak and early enhancement rates, and apparent diffusion coefficient) were compared between the groups.

RESULTS

In total, 63 breast cancer patients and 63 benign breast tumor patients were recruited. MRI detected 53 breast cancer cases and 61 benign breast tumor cases. Molybdenum target X-ray detected 50 breast cancer cases and 60 benign breast tumor cases. The combined methodology detected 61 breast cancer cases and 61 benign breast tumor cases. The sensitivity (96.83%) and accuracy (96.83%) of the combined methodology were higher than single-method MRI (84.13% and 90.48%, respectively) and molybdenum target X-ray (79.37% and 87.30%, respectively) (P < 0.05). The combined methodology specificity (96.83%) did not differ from single-method MRI (96.83%) or molybdenum target X-ray (95.24%) (P > 0.05). The T-wave peak (169.43 ± 32.05) and apparent diffusion coefficient (1.01 ± 0.23) were
Gu WQ et al. Imaging diagnosis of breast cancer

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Grade D (Fair): 0
Grade E (Poor): 0
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INTRODUCTION
Breast cancer can present as multiple malignancies, and recently, the incidence and morbidity are increasing in younger populations[1]. Early-stage breast cancer patients often lack specific clinical manifestations, and without timely diagnosis and intervention, the disease may progress, potentially invading the skin and the thoracic muscles and fascia. For some, undetected malignancies result in lymphatic and distant metastases, which are life-threatening and affect a patient’s quality of life[2-4]. Therefore, early breast cancer diagnosis is critical.

Molybdenum target X-ray examinations are often used to diagnose breast cancer as they have high repeatability and resolution and are noninvasive. However, they have poor penetrability, making satisfactory diagnostic results for deep and high breast cancers difficult[5,6]. Radiological technology is constantly developing, and magnetic resonance imaging (MRI) is also valuable for diagnosing breast cancer; it has high soft-tissue resolution and plainly presents abnormal enhancements in breast images, providing an objective reference for diagnosing and evaluating breast cancer[7].

Therefore, we explored the combined diagnostic efficacy of molybdenum target X-ray and MRI examinations to improve the early detection of breast cancer.

MATERIALS AND METHODS

Patient selection
This study was approved by the Ethics Committee of our hospital. All participating patients and their families provided informed consent. Patients diagnosed with breast cancer at our hospital from March 2019 to April 2021 were recruited, as were the same number of patients diagnosed with benign breast tumors during the same period.

lower in the breast cancer group than in the benign tumor group (228.86 ± 46.51 and 1.41 ± 0.35, respectively). However, the peak enhancement rate (1.08 ± 0.24) and early enhancement rate (1.07 ± 0.26) were significantly higher in the breast cancer group than in the benign tumor group (0.83 ± 0.19 and 0.75 ± 0.19, respectively) (P < 0.05).

CONCLUSION
Combined molybdenum target X-ray and MRI examinations for diagnosing breast cancer improved the diagnostic sensitivity and accuracy, minimizing the missed- and misdiagnoses risks and promoting timely treatment intervention.

Key Words: Molybdenum; X-rays; Magnetic resonance imaging; Breast neoplasms; Early diagnosis; Radiology

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The inclusion criteria were: (1) Pathologically confirmed cancerous or benign tumors; (2) < 80 years of age; (3) The patient had good compliance and communication skills and could cooperate to complete the investigation; (4) An estimated survival time of the breast cancer patients of > 6 mo; and (5) A disease stage of II-IV.

The exclusion criteria were patients with: (1) Other benign or malignant tumors; (2) Cardiovascular or cerebrovascular diseases; (3) Speech communication or hearing disorders; (4) Mental disorders; (5) Allergies; and (6) Contraindications to molybdenum target X-ray or MRI examinations.

All patients in both groups received molybdenum target X-ray and MRI examinations.

**Molybdenum target X-ray examination**

A GE Senographe 2000D Digital Mammography System (GE Healthcare, Chicago, IL, USA) with a molybdenum target X-ray camera and automatic exposure was used. Patients were instructed to stand with their arms up to optimally expose the breast to the X-ray camera. Next, horizontal and axial position breast radiography were performed for a closer examination of specific parameters, such as the breast lesion border, shape, number, and size, to determine if the axillary lymph nodes were enlarged, if there were abnormal blood vessels or microcalcification, and if the tumor lesions had invaded the skin, areola, or nipple.

**MRI examination**

A Magnetom Avanto 3.0T superconducting MRI scanner (Siemens, Munich, Germany) equipped with a special phased-array surface coil for the breast was used. First, the examination procedure was explained to the patient in detail. Then, patients were instructed to take the prone position, placing both breasts into the coil hole on the surface of the special phased array, then resume regular light breathing to minimize image artifacts and decreased image quality caused by chest breathing movements. The axillary position of the breast was placed into the coil as far as possible, and an auxiliary fixation device was used to pressurize the breast. A plain MRI was performed first. The sagittal and horizontal axial positions of the left and right mammary glands were obtained using the T1-weighted image (T1WI) spin-echo sequence, an echo time (TE) of 15 ms, and a repetition time (TR) of 580 ms. A short-time reversal recovery sequence was added to the T2WI turbo spin-echo sequence. The interval was 0.6 mm with a 3-mm-thick layer, and the inversion time (i.e., Ti) was 230 ms, TE was 56 ms, and TR was 4820 ms. Next, dynamic enhanced MRI scanning was performed using T1WI axial scanning with fat suppression and rapid small-angle excitation of the three-dimensional dynamic imaging sequence, repeated six times. The parameters were: 55 s single scan, a 296 × 384 matrix, 104 Layers, 0.9-mm layer thickness, 1.7 ms TE, and 4.6 ms TR. A special double-tube high-pressure syringe was used to inject 0.15 mmol/kg gadolinium-dextran solution at a rate of 2 mL/s through the cubital vein.

The images were transferred to MRI workstation software for reconstruction. The maximum signal projections of the images were analyzed before and after enhancement. The area of interest in the lesions was manually selected to ensure that the MRI on the same plane was within the range of the lesions. To prevent errors, a minimum area of 2 mm² was used to avoid necrosis or cystic components in the lesions. Two physicians with considerable diagnostic experience examined the radiographs together, and the MRI and molybdenum target X-ray examinations were analyzed with emphasis on the number, location, shape, and size of the lesions.

**Observation indexes**

The examination conditions, diagnostic efficacy parameters (e.g., the sensitivity, specificity, and accuracy), and examination parameters (e.g., T-wave peak, peak and early enhancement rates, and apparent diffusion coefficient) were compared between the breast cancer and benign tumor groups based on the diagnosis methodology [single-method (X-ray or MRI) or combined-method (both X-ray and MRI)].

**Statistical analyses**

Data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Measurement data were analyzed by t-test and represented by means ± SD. Enumerated data were analyzed by the χ² test and represented as n (%). Statistical significance was set at P < 0.05.
RESULTS

Patient demographics
In our hospital, 63 patients were diagnosed with breast cancer from March 2019 to April 2021 and were included in the study, along with 63 patients diagnosed with benign breast tumors during the same period. The mean age of the breast cancer group was 58.32 ± 10.77 years (range, 44-73 years). There was 1 mucinous carcinoma case, 2 intraductal carcinoma cases, and 60 invasive ductal carcinoma cases. Regarding the disease stage, 24 cases were stage II, 21 were stage III, and 18 were stage IV. There were 39 cases with lymph node metastasis and 24 with no metastasis. A total of 31 cases were highly differentiated, 15 were moderately differentiated, and 17 were poorly differentiated.

The mean age of the benign tumor group was 60.03 ± 11.38 years (range, 42–76 years). There were 43 fibroadenoma cases, 13 intraductal papilloma cases, and 7 lobular tumor cases.

The baseline data, such as age, did not differ between the two groups (P > 0.05).

Molybdenum target X-ray and MRI examination conditions
MRI detected 53 breast cancer cases and 61 benign breast tumor cases. Molybdenum target X-ray detected 50 breast cancer cases and 60 benign breast tumor cases. The combined methodology detected 61 breast cancer cases and 61 benign breast tumor cases (Table 1).

Diagnostic efficacy
The sensitivity (96.83%) and accuracy (96.83%) of the combined methodology were higher than the single-method molybdenum target X-ray (79.37% and 87.30%, respectively) and MRI (84.13% and 90.48%, respectively) (P < 0.05). However, the combined methodology specificity (96.83%) did not differ from single-method molybdenum target X-ray (95.24%) or MRI (96.83%) (P > 0.05) (Table 2).

MRI-related examination parameters
The T-wave peak and apparent diffusion coefficient were lower in the breast cancer group (169.43 ± 32.05 and 1.01 ± 0.23, respectively) than in the benign tumor group (228.86 ± 46.51 and 1.41 ± 0.35, respectively). However, the peak early enhancement rates (1.08 ± 0.24 and 1.07 ± 0.26, respectively) were significantly higher in the breast cancer group than in the benign tumor group (0.83 ± 0.19 and 0.75 ± 0.19, respectively; P < 0.05) (Table 3).

DISCUSSION
Breast cancer has a relatively high morbidity rate among females due to lacking specific clinical manifestations in the early stages, resulting in very high missed- and misdiagnosis rates. There is also adhesion between the lesion and surrounding tissue, and a lack of good activity, easily leading to negative palpation[8]. Therefore, identifying more exact breast cancer diagnosis methods remains a key topic.

Molybdenum target X-ray is a common low-cost, simple to operate diagnostic measure that can effectively identify the breast lesion’s edge morphology and clarify the breast tissue density. However, the breast volume of Asian females is smaller with higher density than other populations, making a cancer diagnosis easy to miss due to the lack of good wrapping in the molybdenum target X-ray photography process. Moreover, X-ray examination emits a certain amount of radiation, leading to clinical application limitations[9,10]. It is also difficult to distinguish tumor infiltration and the margin of fibrous tissue proliferation by molybdenum target X-ray, thus disturbing the testing and evaluation conditions of breast lesions. Further, molybdenum target X-ray examination usually adopts an axial or head-to-tail projection, but the maximum diameter of breast lesions may be in an oblique position, which can affect the detection of the tumor’s maximum diameter, consequently underestimating the size[11].

There are also many heterogeneous and tanglesome new blood vessels in breast cancer tissue, consisting of an incomplete fissure vascular network without relaxation and contraction, making it easy to unusually enhance the microvascular permeability, tissue gap volume, microcirculation flow, and velocity on a molybdenum target X-ray image. The incidence and progression of breast cancer are closely related to an incomplete vascular network[12]. Through intravenous injections of contrast dye with
Table 1 Molybdenum target X-ray and magnetic resonance imaging combined methodology examination conditions

<table>
<thead>
<tr>
<th>Pathological result</th>
<th>MRI</th>
<th>Both</th>
</tr>
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<tbody>
<tr>
<td>X-ray</td>
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<td></td>
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<tr>
<td>+</td>
<td>50</td>
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<td>63</td>
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<tr>
<td>Total</td>
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MRI: Magnetic resonance imaging.

Table 2 Molybdenum target X-ray and magnetic resonance imaging diagnostic efficacies

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molybdenum target X-ray</td>
<td>79.37% (50/63)</td>
<td>95.24% (60/63)</td>
<td>87.30% (110/126)</td>
</tr>
<tr>
<td>MRI</td>
<td>84.13% (53/63)</td>
<td>96.83% (61/63)</td>
<td>90.48% (114/126)</td>
</tr>
<tr>
<td>Combined methodology</td>
<td>96.83% (61/63)</td>
<td>96.83% (61/63)</td>
<td>96.83% (122/126)</td>
</tr>
</tbody>
</table>

$\chi^2/P$ value (Combined vs molybdenum target X-ray)

<table>
<thead>
<tr>
<th>$\chi^2/P$ value (Combined vs MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.568/0.006</td>
</tr>
<tr>
<td>0.000/1.000</td>
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<tr>
<td>6.572/0.010</td>
</tr>
</tbody>
</table>

MRI: Magnetic resonance imaging.

Table 3 Magnetic resonance imaging-related examination parameters (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>T-wave peak</th>
<th>Apparent diffusion coefficient</th>
<th>Peak enhancement rate</th>
<th>Early enhancement rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer ($n = 63$)</td>
<td>169.43 ± 32.05</td>
<td>1.01 ± 0.23</td>
<td>1.08 ± 0.24</td>
<td>1.07 ± 0.26</td>
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<tr>
<td>Benign tumor ($n = 63$)</td>
<td>228.86 ± 46.51</td>
<td>1.41 ± 0.35</td>
<td>0.83 ± 0.19</td>
<td>0.75 ± 0.19</td>
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<td>$t$ value</td>
<td>8.351</td>
<td>7.581</td>
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<td>7.887</td>
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<td>$P$ value</td>
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<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

MRI: Magnetic resonance imaging.

In a high-pressure syringe, MRI examination can effectively identify breast cancer lesions. Thus, it is possible to analyze and evaluate the hemodynamic characteristics of breast lesions to provide an objective reference for diagnosing and evaluating breast cancer based on the blood vessels distribution in the lesions[13]. However, there are still some limitations to diagnosing only by MRI; it has low sensitivity to common micro-needle calcifications in the early stages of breast cancer and the image quality is easily affected by several factors, such as respiratory artifacts and heartbeats[14].

Our study diagnosed breast cancer using molybdenum target X-ray and MRI examinations together and found that both T-wave peak and apparent diffusion coefficient were lower in the breast cancer group than in the benign tumor group, yet the peak and early enhancement rates were significantly higher in the breast cancer group than in the benign tumor group. The combined methodology sensitivity and accuracy were also significantly higher than either single method. These results suggest that each method has particular strengths but using both methods together enhance the diagnostic sensitivity and accuracy and reduce the risk of missed diagnosis and misdiagnosis. Several reasons may explain our results. First, molybdenum target mammography of the breast includes full-screen digital mammography and digital tomography synthetic mammography, which has been further developed in recent years and is highly sensitive to calcification, which is important for the screening and early diagnosis of breast cancer. However, in patients with dense breast cancer, the lesions are easy to cover, and the penetrating power of the molybdenum target X-ray is limited. Therefore, tiny lesions in deep glands are easily overlooked, resulting in missed diagnoses. However, an advantage to
molybdenum target X-ray examination is the ability to accurately examine microcalcifications\[15\].

Second, MRI accurately identifies soft tissue and then presents the tumor lesions in a multi-image and multi-directional manner. Further, it does not induce radiation damage to the body, guaranteeing patient safety. MRI can also improve the accuracy of detecting breast cancer lesions, judge dense breast tumors, perform differential diagnosis between fibrous scar and local recurrence after surgery, examine multicenter and concealing venereal lesions, and dynamically examine the blood supply around the lesion. Kuhl\[16\] reported that MRI examinations helped detect bilateral breast lesions by achieving three-dimensional localization of the breast and tumor, accurately measuring the distance between the breast tumor and the areola, and identifying the invasion of breast lesions to tissue. However, some reports found a significantly higher multifocal and axillary lymph node metastasis and peripheral invasion detection rate by MRI, compared to molybdenum target X-ray, but the detection rate of extensive microcalcification lesions was lower by MRI than by molybdenum target X-ray. Therefore, the advantages and disadvantages of the combined methodology are complementary and improve the overall sensitivity and accuracy\[17\]. However, the results of this study are limited by the nature of this being a single center study, and must be further clarified by a multi-center alliance.

CONCLUSION

Combined molybdenum target X-ray and MRI examinations improved the sensitivity and accuracy of breast cancer diagnoses, minimizing the missed- and misdiagnoses risks and promoting timely treatment intervention.

ARTICLE HIGHLIGHTS

Research background
The incidence of breast cancer among young people has been on the rise in recent years.

Research motivation
Early breast cancer diagnosis is critical.

Research objectives
Explore more sensitive and accurate breast cancer screening methods.

Research methods
 Patients diagnosed with breast cancer at our hospital were recruited, as were the same number of patients diagnosed with benign breast tumors during the same period.

Research results
The combined methodology detected 61 breast cancer cases and 61 benign breast tumor cases. The sensitivity (96.83\%) and accuracy (96.83\%) of the combined methodology were higher than single-method magnetic resonance imaging (MRI) (84.13\% and 90.48\%, respectively) and molybdenum target X-ray (79.37\% and 87.30\%, respectively).

Research conclusions
Combined molybdenum target X-ray and MRI examinations for diagnosing breast cancer improved the diagnostic sensitivity and accuracy.

Research perspectives
Early diagnosis of cancer is very important, we need to find more early cancer diagnosis methods in the future.
Biomed Health Inform

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Different MRI protocols: A meta-analysis.

Martaindale SR


Retrospective Study

Value of thyroglobulin combined with ultrasound-guided fine-needle aspiration cytology for diagnosis of lymph node metastasis of thyroid carcinoma

Liu-Yang Zhang, Yong Chen, Ya-Zhou Ao

ORCID number: Liu-Yang Zhang 0000-0003-4367-5713; Yong Chen 0000-0001-8014-7683; Ya-Zhou Ao 0000-0003-3195-5814.

Author contributions: Zhang LY and Chen Y designed the research study; Zhang LY and Ao YZ performed the research, analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Affiliated Hospital of Chengde Medical College Institutional Review Board.

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

Conflict-of-interest statement: There is no conflict of interest.

Data sharing statement: No additional data are available.

Supported by: The Research and Development Project of Science and Technology of Chengde City, Liu-Yang Zhang, Yong Chen, Ya-Zhou Ao, Department of Thyroid Surgery, Affiliated Hospital of Chengde Medical University, Chengde 067000, Hebei Province, China

Corresponding author: Yong Chen, BM BCh, Chief Physician, Department of Thyroid Surgery, Affiliated Hospital of Chengde Medical University, No. 36 Nanyingzi Street, Shuangqiao District, Chengde 067000, Hebei Province, China. chenyong2021@yeah.net

Abstract

BACKGROUND
Surgery for thyroid carcinoma offers a good prognosis; however, cervical lymph node metastasis may occur in the early stage. An effective diagnostic method can accurately guide clinical surgical planning and the scope of lymph node dissection, ultimately improving patient prognosis.

AIM
To explore the diagnostic value of fine-needle aspiration of thyroglobulin (FNA-Tg) combined with ultrasound (US)-guided fine-needle aspiration cytology for cervical lymph node metastasis in thyroid carcinoma.

METHODS
We enrolled 209 pathologically confirmed thyroid carcinoma patients who visited our hospital between Jan 2017 and Dec 2020. Patients were tentatively diagnosed with cervical lymph node enlargement using preoperative US. They underwent US-guided fine-needle aspiration cytology and FNA-Tg. The value of single and combined application of the two methods for the diagnosis of cervical lymph node metastasis was calculated. The factors affecting FNA-Tg for diagnosis were analyzed using univariate and multivariate methods.

RESULTS
FNA-Tg values were significantly higher among patients with positive cervical lymph node metastasis. The sensitivity and specificity of US-guided fine-needle aspiration cytology, FNA-Tg, and US-guided fine-needle aspiration cytology + FNA-Tg were 85.48% and 90.59%, 83.06% and 87.06%, and 96.77% and 91.76%, respectively. The area under the receiver operating characteristic curve for US-guided fine-needle aspiration cytology, FNA-Tg, and the two combined, was 0.880, 0.851, and 0.943, respectively. A long diameter/short diameter ratio < 2, an
INTRODUCTION

Common clinical diagnostic methods for cervical lymph node metastasis in thyroid carcinoma patients include ultrasound (US), computed tomography, magnetic resonance imaging, radionuclide scanning, and other imaging methods, as well as US-guided fine-needle aspiration cytology (FNAC). However, all of these methods have limitations. US is the most commonly used imaging method; however, comorbid inflammatory lymphadenopathy can lead to misdiagnosis; accurate differentiation between benign and malignant nodules requires extensive experience. FNAC can offer further cytological diagnostic support for lymph nodes with suspicious US results. However, incorrect sampling sites, insufficient sample sizes, small metastases, and cystic alteration of the lesion can lead to false-negative results. Fine-needle aspiration of thyroglobulin (FNA-Tg) has relatively high diagnostic value in lymph node metastasis and recurrence of differentiated thyroid carcinoma. FNA-Tg combined with ultrasonic-guided fine-needle aspiration cytology has a certain meaning in the thyroid carcinoma with lymph node metastasis.

MATERIALS AND METHODS

Data

A total of 209 pathologically diagnosed thyroid carcinoma patients who visited the Thyroid Surgery Department of Affiliated Hospital of Chengde Medical University between Jan 2017 and Dec 2020 were selected. The inclusion criteria were as follows: (1) Patients who met the diagnostic criteria of thyroid cancer according to the National Comprehensive Cancer Network Guidelines for thyroid cancer criteria; (2) Patients with confirmed pathological diagnosis; (3) Patients aged 20 to 67 years; (4) Patients who presented with suspicious lymph node enlargement on preoperative cervical lymph node US and then underwent US-guided FNAC and FNA-Tg; and (5) Patients with complete data. The exclusion criteria were as follows: (1) Patients with a history of radiotherapy and chemotherapy; and (2) Patients with lung infections and heart failure.
Before the implementation of this study, the research plan was submitted to the Medical Ethics Committee of our hospital for approval and then implemented after the decision and document of the Medical Ethics Committee.

**Instrument check and FNAC method**
For FNAC, the patients were placed supine with a soft pillow under their neck to fully expose the puncture site. After routine disinfection of the puncture site, 1% lidocaine was applied under local anesthesia. A 22 G cell puncture needle (Yako, Japan) was selected, and the fine needle was inserted into the center of the lymph node under US guidance. The needle was rapidly retracted and inserted back and forth in different needle channels five times. Subsequently, the puncture needle was pulled out, the aspirated tissue was placed onto the slide, smeared, and fixed for pathological examination. Each lymph node was punctured at least three times. After HE staining, the smears were reviewed by two senior pathologists, and the cancer cells were either determined to be positive for lymph node metastases, or if no cancer cells were found, or if the number of cells was insufficient, the cells were determined to be negative.

**FNA-Tg testing method**
For FNA-Tg measurement, 0.5 mL of 0.9% normal saline was absorbed with a 1-mL syringe, the needle was rinsed, and 1 mL of eluent was prepared. The supernatant was extracted after centrifugation at 3000 r/min for 5 min. Subsequently, the Tg content was detected using the COBAS E601 electrochemical analyzer (Roche, Basel, Switzerland) and an immunochemiluminescence method.

The judgment standards[7] were as follows: FNA-Tg > 1.0 ng/mL was diagnosed as positive thyroid cancer lymph node metastasis, and FNA-Tg ≤ 1.0 ng/mL was diagnosed as negative thyroid cancer lymph node metastasis.

**Statistical analyses**
In this study, age and other measurement indexes were tested for normal distribution, and all were in line with approximate normal distribution or normal distribution, which was expressed by mean ± SD. A t-test was performed using SPSS software (IBM Corp., Armonk, NY, USA). The measured data were analyzed using an χ² test. For multivariate analysis, a logistic regression model was used to draw the ROC curve and obtain the area under the curve (AUC). The test level was α = 0.05.

### RESULTS

**Ultrasonographic findings of cervical lymph node metastases in positive and negative patients**
On US, patients with positive cervical lymph node metastasis showed significantly higher rates of cortical centripetal thickening, hypoechogenicity of the cortex and the medulla, long diameter/short diameter ratio < 2, partial liquefaction or fusion of lymph nodes, abundant internal blood supply, and hilar absence than patients with negative lymph node metastasis (P < 0.05) (Table 1).

**Comparison of FNA-Tg values in positive and negative patients with cervical lymph node metastasis**
FNA-Tg values were significantly higher in patients with positive cervical lymph node metastasis than those with negative lymph node metastasis (P < 0.05) (Table 2).

**Value of FNAC alone and FNA-Tg alone and their combination for the diagnosis of cervical lymph node metastasis in patients with thyroid carcinoma**
Considering pathological results as the gold standard, a four-grid table was prepared (Table 3). The sensitivity and specificity of FNAC in the diagnosing cervical lymph node metastasis of thyroid carcinoma were 85.48% and 90.59%, respectively. The sensitivity and specificity of FNA-Tg for diagnosing cervical lymph node metastasis of thyroid carcinoma were 83.06% and 87.06%, respectively. The sensitivity and specificity of FNAC + FNA-Tg for diagnosing cervical lymph node metastasis of thyroid carcinoma were 96.77% and 91.76%, respectively (Table 4).

Figure 1 shows the results of US-guided FNA examination of cervical lymph nodes and postoperative pathological examination of lymph nodes in patients with papillary thyroid carcinoma with positive lymph node metastasis.
Table 1 Ultrasonographic findings of cervical lymph node metastases in positive and negative patients, n (%)

<table>
<thead>
<tr>
<th>Pathological results</th>
<th>n</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
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<th>Yes</th>
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<td>55</td>
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</tbody>
</table>

**ROC curve analysis of FNAC and FNA-Tg alone and in combination for diagnosis of cervical lymph node metastasis in thyroid carcinoma patients**

An ROC curve was drawn adopting the pathological results as the gold standard. Results showed that the AUC value for FNAC diagnosis of thyroid carcinoma with cervical lymph node metastasis was 0.880. The AUC value for FNA-Tg diagnosis of thyroid carcinoma with cervical lymph node metastasis was 0.851. The AUC value for FNAC + FNA-Tg for diagnosing thyroid carcinoma with cervical lymph node metastasis was 0.943 (Figure 2).

**Univariate analysis of the influence of FNA-Tg alone on the diagnosis of cervical lymph node metastasis in patients with thyroid carcinoma**

Patients were divided into groups based on FNA-Tg differential diagnosis. The univariate analysis showed that the differences between the two groups were statistically significant (P < 0.05), including the rate of long diameter, long diameter/short diameter lymph node ratio, the number of collected cells, serum thyroid stimulating hormone (TSH), serum Tg, and US characteristics (Table 5).

**Multivariate analysis of the influence of FNA-Tg on the single diagnosis of cervical lymph node metastasis in patients with thyroid carcinoma**

The results of FNA-Tg differential diagnosis of cervical lymph node metastasis were adopted as dependent variables, and the statistically significant indexes, such as long diameter, long diameter/short diameter lymph node ratio, the number of collected cells, serum TSH, serum Tg, and characteristics of US signs, were adopted as independent variables to establish a logistic regression model. A long diameter/short diameter ratio < 2, insufficient number of acquired cells, low level of serum Tg, and absence of typical US signs of lymph node metastasis were found to increase the risk of cervical lymph node metastasis in patients with thyroid carcinoma misdiagnosed...
Table 2 Comparison of fine-needle aspiration thyroglobulin values between positive and negative patients with cervical lymph node metastasis (mean ± SD)

<table>
<thead>
<tr>
<th>Pathological results</th>
<th>n</th>
<th>FNA-Tg (ng/mL)</th>
<th>t value</th>
<th>P value</th>
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<tbody>
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<td>Positive cervical lymph node metastasis</td>
<td>124</td>
<td>1.56 ± 0.47</td>
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<td>0.000</td>
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<tr>
<td>Negative cervical lymph node metastasis</td>
<td>85</td>
<td>0.77 ± 0.21</td>
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</table>

FNA-Tg: Fine-needle aspiration thyroglobulin.

Table 3 The comparison of pathological diagnosis results between single and combined diagnosis of fine-needle aspiration and fine-needle aspiration thyroglobulin

<table>
<thead>
<tr>
<th>FNA</th>
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<th>Negative</th>
<th>Total</th>
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</table>

<table>
<thead>
<tr>
<th>Pathological results</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNA-Tg</td>
<td>Positive</td>
<td>103</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>21</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>124</td>
<td>85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathological results</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNA + FNA-Tg</td>
<td>Positive</td>
<td>120</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>4</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>124</td>
<td>85</td>
</tr>
</tbody>
</table>

FNA: Fine-needle aspiration; FNA-Tg: Fine-needle aspiration thyroglobulin.

Table 4 Value of fine-needle aspiration and fine-needle aspiration thyroglobulin alone and in combination in the diagnosis of cervical lymph node metastasis in patients with thyroid carcinoma (%)

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Rate of missed diagnosis</th>
<th>Misdiagnosis rate</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNA</td>
<td>85.48</td>
<td>90.59</td>
<td>14.52</td>
<td>9.41</td>
<td>92.98</td>
<td>81.05</td>
</tr>
<tr>
<td>FNA-Tg</td>
<td>83.06</td>
<td>87.06</td>
<td>16.94</td>
<td>12.94</td>
<td>90.35</td>
<td>77.89</td>
</tr>
<tr>
<td>FNA + FNA-Tg</td>
<td>96.77</td>
<td>91.76</td>
<td>3.23</td>
<td>8.24</td>
<td>94.49</td>
<td>95.12</td>
</tr>
</tbody>
</table>

FNA: Fine-needle aspiration; FNA-Tg: Fine-needle aspiration thyroglobulin.

using FNA-Tg (P < 0.05) (Table 6).

**DISCUSSION**

Our study showed that patients with positive cervical lymph node metastasis had significantly higher rates of cortical centripetal thickening, hypoechoigenicity of the cortex and medulla, long diameter/short diameter ratio < 2, partial liquefaction or fusion of lymph nodes, abundant internal blood supply, and hilar absence than patients with negative lymph node metastasis (P < 0.05). These are the typical US characteristics of lymph node metastasis. The normal oval structure of the lymph nodes can be destroyed by the cancer cells; they have an irregular or round shape with a change in the vertical and horizontal diameter ratio. The internal structure can also be destroyed. In the case of lymph node metastasis, the lymphadenocortex involvement occurs first, leading to the loss of the cutaneous medulla structure. Moreover, the infiltration of cancer cells destroys the normal blood supply to the lymph nodes, and US usually reveals an uneven blood supply to the lymph nodes.

Tg is secreted by normal thyroid tissue and differentiated thyroid carcinoma and is a marker of tumor protein in peripheral blood[8,9]. Tg expression is negligible in normal lymph nodes; d, it can be expressed in differentiated thyroid carcinoma, and lymph node metastasis and its concentration in tissue puncture fluid are much higher than that in serum[10]. Detecting FNA-Tg levels in the eluent of needle biopsy samples can help reach the differential diagnosis of cervical lymph node metastasis in thyroid carcinoma. In this study, we adopted specific reference values for detecting positive
Table 5 Univariate analysis of influence of fine-needle aspiration thyroglobulin on the single diagnosis of cervical lymph node metastasis in patients with thyroid carcinoma

<table>
<thead>
<tr>
<th>Index</th>
<th>Correct diagnosis (n = 177)</th>
<th>Error diagnosis (n = 32)</th>
<th>t/χ² value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.3 ± 5.8</td>
<td>48.2 ± 6.6</td>
<td>0.966</td>
<td>0.335</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>67 (37.85)</td>
<td>11 (34.38)</td>
<td>0.140</td>
<td>0.708</td>
</tr>
<tr>
<td>Female</td>
<td>110 (62.15)</td>
<td>21 (65.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short diameter of lymph node (cm)</td>
<td>0.62 ± 0.11</td>
<td>0.60 ± 0.08</td>
<td>0.982</td>
<td>0.327</td>
</tr>
<tr>
<td>Long diameter of lymph node (cm)</td>
<td>1.38 ± 0.20</td>
<td>1.29 ± 0.23</td>
<td>2.288</td>
<td>0.023</td>
</tr>
<tr>
<td>Long diameter/short diameter, n (%)</td>
<td></td>
<td></td>
<td>6.965</td>
<td>0.008</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>88 (49.72)</td>
<td>24 (75.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>89 (50.28)</td>
<td>8 (25.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of collected cells, n (%)</td>
<td></td>
<td></td>
<td>15.034</td>
<td>0.000</td>
</tr>
<tr>
<td>Insufficient</td>
<td>11 (6.21)</td>
<td>9 (28.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sufficient</td>
<td>166 (93.79)</td>
<td>23 (71.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum TSH (ng/mL)</td>
<td>2.09 ± 0.39</td>
<td>2.31 ± 0.46</td>
<td>-2.854</td>
<td>0.005</td>
</tr>
<tr>
<td>Serum TgAb (IU/mL)</td>
<td>20.83 ± 5.17</td>
<td>22.15 ± 5.83</td>
<td>-1.303</td>
<td>0.194</td>
</tr>
<tr>
<td>Serum Tg (ng/mL)</td>
<td>18.94 ± 4.20</td>
<td>16.84 ± 4.00</td>
<td>2.621</td>
<td>0.009</td>
</tr>
<tr>
<td>Number of cervical lymph node metastases</td>
<td>3.41 ± 0.84</td>
<td>3.15 ± 0.76</td>
<td>1.634</td>
<td>0.104</td>
</tr>
<tr>
<td>Characteristics of ultrasonic signs, n (%)</td>
<td></td>
<td></td>
<td>4.885</td>
<td>0.027</td>
</tr>
<tr>
<td>Signs of metastasis</td>
<td>142 (80.23)</td>
<td>20 (62.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No signs of metastasis</td>
<td>35 (19.77)</td>
<td>12 (37.50)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TSH: Thyroid stimulating hormone; Tg: Thyroglobulin.

Table 6 Logistic model of the influencing factors in fine-needle aspiration thyroglobulin diagnosis of lymph node metastasis

<table>
<thead>
<tr>
<th>Factors</th>
<th>SE</th>
<th>Walds</th>
<th>P value</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long diameter of lymph node</td>
<td>0.611</td>
<td>2.199</td>
<td>0.138</td>
<td>1.842</td>
<td>0.822</td>
</tr>
<tr>
<td>Long diameter/short diameter</td>
<td>0.741</td>
<td>4.806</td>
<td>0.041</td>
<td>2.098</td>
<td>1.082</td>
</tr>
<tr>
<td>Number of collected cells</td>
<td>-0.612</td>
<td>4.275</td>
<td>0.047</td>
<td>0.542</td>
<td>0.304</td>
</tr>
<tr>
<td>Serum TSH</td>
<td>0.285</td>
<td>1.725</td>
<td>0.216</td>
<td>1.330</td>
<td>0.869</td>
</tr>
<tr>
<td>Serum Tg</td>
<td>-0.442</td>
<td>5.647</td>
<td>0.025</td>
<td>1.556</td>
<td>1.081</td>
</tr>
<tr>
<td>Characteristics of ultrasonic signs</td>
<td>0.804</td>
<td>5.044</td>
<td>0.037</td>
<td>2.234</td>
<td>1.108</td>
</tr>
<tr>
<td>Constant term</td>
<td>1.309</td>
<td>3.662</td>
<td>0.091</td>
<td>3.702</td>
<td>0.969</td>
</tr>
</tbody>
</table>

TSH: Thyroid stimulating hormone; Tg: Thyroglobulin; OR: Odds ratio.

lymph node metastasis using FNA-Tg. The FNA-Tg value was significantly higher in patients with positive lymph node metastasis than patients with negative lymph node metastasis (P < 0.05). This suggests that because the thyroid tissue has a secretory function in the lymph node tissue, it may appear as lymph node metastasis due to the biological characteristics of the cell. Currently, FNAC is considered the most direct method to diagnose lymph node properties, as it can directly obtain the cells of the lesion and its tissue. However, its smear can be affected by factors such as blood, glia, and cell count, leading to a low sensitivity [10-12]. When the lymph nodes are too small and the smear cells are insufficient, the sensitivity and specificity of FNAC diagnosis can be reduced, leading to an increase in false negatives, affecting the clinical
diagnostic efficiency, and reducing the predictive accuracy[13].

Affected by many factors, the positive threshold of FNA-Tg remains controversial [14,15]. Although previous studies have reported that the diagnostic sensitivity of FNA-Tg was better than that of FNAC[16], our results showed no significant difference in sensitivity between the two methods. The small sample size in this study might have affected the sensitivity and specificity of the results. We found that the sensitivity and specificity of FNAC + FNA-Tg were superior for the diagnosis of cervical lymph node metastasis, thereby providing higher diagnostic accuracy. This may be because metastatic lymph nodes in thyroid carcinoma may be accompanied by significant cystic changes, which could be easily missed by FNAC examination alone. Lymph node eluting fluid has high Tg expression, which is of great help to the diagnosis. Cervical lymphoid node enlargement has many causes, and cytological examination alone is often insufficient for making a precise diagnosis. However, if combined with eluent FNA-Tg examination, the accuracy of diagnosis is improved.

In this study, a univariate analysis of the influence of FNA-Tg findings on the diagnosis of cervical lymph node metastasis revealed a significant difference between the two groups ($P < 0.05$) in terms of the rate of long diameter, the long diameter/short diameter ratio of the lymph nodes, the number of collected cells, serum TSH
level, serum Tg level, and US characteristics. The multivariate analysis showed that a long diameter/short diameter ratio of < 2, an insufficient amount of acquired cells, low level of serum Tg, and absence of typical US signs increased the risk of cervical lymph node metastasis in patients with thyroid carcinoma misdiagnosed by FNA-Tg ($P < 0.05$).

Some studies\cite{17} have reported that the loss of thyroid tissue and inhibition of serum TSH after thyroidectomy may decrease serum Tg levels, and the levels of serum Tg can independently influence the diagnosis of FNA-Tg. Inhibition of serum TSH can reduce the serum Tg level, and a false negative FNA-Tg diagnosis is possible. In contrast, when serum Tg is not reduced, a false positive FNA-Tg diagnosis is possible \cite{18}. Therefore, it is suggested that FNA-Tg should be tested after TSH stimulation. The diagnostic performance of the FNA-Tg diagnostic threshold varies with thyroid status and serum Tg concentration, but there is no doubt that FNA-Tg detection as an auxiliary diagnostic method can bring about all of its unique advantages.

In this study, patients with suspicious cervical lymph node findings on US were studied. FNAC and FNA-Tg were performed to determine whether or not the diagnosis was thyroid lymph node metastatic carcinoma. Compared with previous studies\cite{19,20}, in our study, univariate and multivariate analyses of factors affecting FNA-Tg diagnosis were conducted for the first time, and the results were highly reliable. However, there were also some limitations to our study. The detection process and threshold setting lacked unified standards. Moreover, the factors affecting the test results were numerous and unclear. Thyroid inflammation, autoimmune diseases, and endocrine system diseases can all affect the serum Tg determination to some extent, especially in patients with false-positive and false-negative results. Therefore, underlying diseases should also be considered.

**CONCLUSION**

In conclusion, when diagnosing thyroid carcinoma patients with cervical lymph node metastasis, FNA-Tg can be affected by various factors, and its diagnostic value alone is not high; however, combined with FNAC, the sensitivity and specificity of diagnosis are significantly improved, providing a significant reference value to guide the treatment.

**ARTICLE HIGHLIGHTS**

**Research background**
Fine-needle aspiration cytology (FNAC) can offer further cytological diagnostic support for lymph nodes with suspicious ultrasound (US) results.

**Research motivation**
Fine-needle aspiration of thyroglobulin (FNA-Tg) reportedly has a relatively high diagnostic value in lymph node metastasis and recurrence of differentiated thyroid carcinoma.

**Research objectives**
We explore and describe the value of FNA-Tg combined with US-guided FNAC to diagnose cervical lymph node metastasis in patients with thyroid carcinoma.

**Research methods**
A total of 209 pathologically diagnosed thyroid carcinoma patients who visited the Thyroid Surgery Department of the Hospital were selected.

**Research results**
The sensitivity and specificity of US-guided FNAC, FNA-Tg, and US-guided FNAC + FNA-Tg were 85.48% and 90.59%, 83.06% and 87.06%, and 96.77% and 91.76%, respectively.

**Research conclusions**
Combined with US-guided FNAC, it is significantly improved.
The detection process and threshold setting lacked unified standards.

REFERENCES


Zhang LY et al. Diagnosis of lymph node metastasis in thyroid cancer

6-13 [PMID: 23090642 DOI: 10.1097/CCO.0b013e32835a9ab1]


Retrospective Study

Locking compression plate + T-type steel plate for postoperative weight bearing and functional recovery in complex tibial plateau fractures

Hai-Feng Li, Tao Yu, Xing-Fei Zhu, Hua Wang, Ying-Qi Zhang

ORCID number: Hai-Feng Li 0000-0002-0856-9782; Tao Yu 0000-0002-7537-6710; Xing-Fei Zhu 0000-0002-1064-6628; Hua Wang 0000-0002-2986-0261; Ying-Qi Zhang 0000-0002-4616-6888.

Author contributions: Li HF and Yu T designed this retrospective study, Li HF, Yu T and Zhu XF wrote this paper; Li HF, Yu T, Zhu XF, Wang H and Zhang YQ were responsible for sorting the data.

Institutional review board statement: The study was reviewed and approved by the Tongji Hospital Institutional Review Board.

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

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

Data sharing statement: No additional data are available.

Country/Territory of origin: China

Hai-Feng Li, Tao Yu, Xing-Fei Zhu, Ying-Qi Zhang, Department of Orthopaedic Surgery, Tongji Hospital, School of Medicine, Tongji University, Shanghai 200065, China

Hua Wang, Department of Orthopaedic Surgery, Zhabei Central Hospital, Shanghai, Shanghai 200070, China

Corresponding author: Hai-Feng Li, MD, Associate Professor, Department of Orthopaedic Surgery, Tongji Hospital, School of Medicine, Tongji University, No. 389 Xincun Road, Shanghai 200065, China. lihaifeng501@163.com

Abstract

BACKGROUND

Complex tibial plateau fractures can seriously affect quality of life and physical and mental health of patients. The anatomical relationship between the proximal tibial bone and soft tissue is complex, resulting in different types of tibial plateau fractures. Violent trauma can lead to displaced fracture, serious soft tissue injury, and potentially, dislocation of the knee joint. Therefore, tibial plateau fractures are extremely unstable.

AIM

To assess the use of locking compression plate (LCP) + T-type steel plate for postoperative weight bearing and functional recovery of complex tibial plateau fractures.

METHODS

Ninety-seven patients with complex tibial plateau fractures who underwent surgery at our hospital were selected for retrospective study. Forty-nine patients had been treated with LCP + T-type steel plate limited internal fixation (study group), and 48 patients with bilateral ordinary steel plate support (control group). The operation process index, postoperative rehabilitation related index, Rasmussen score of the knee joint, tibial plateau varus angle (TPA), tibial plateau retroversion angle (PA), and surgical complications of the two groups were compared.

RESULTS

The operation time and intraoperative bone graft volume in the study group were
INTRODUCTION

Tibial plateau fracture is one of the most common types of fractures in clinical practice. It is frequently caused by violent trauma to the tibial plateau that results in the fracture and even articular surface collapse. It can be accompanied by serious knee varus and joint instability, which has a major impact on the activity and function of the knee joint. Patients with complex tibial plateau fractures are prone to developing skin necrosis, incision site infection, and joint instability after surgery; thus, early active treatment is needed[1]. The clinical treatment criteria for complex tibial plateau fractures recommends anatomical reduction, firm and stable fixation, and early training. Currently, operational treatment requires good biomechanical function, anatomical reduction of the articular surface, and reduction of soft tissue damage. In the past, double plate internal fixation was used in clinical practice; however, the procedure involved adjunct stripping of soft tissue, resulting in increased postoperative complications[2,3]. Clinical application of the locking plate can not only reduce damage to the soft tissue but also the incidence of postoperative necrosis. However, the stability of the articular surface fixed with a locking steel plate alone, cannot be guaranteed[4]. In this study, locking compression plate (LCP) + T-shaped steel plate limited internal fixation was used to treat complex tibial plateau fractures to find a more reliable internal fixation method for use in clinical practice.

Core Tip: Locking compression plate + T-type steel plate limited internal fixation treatment has the advantage of less trauma and enables early postoperative functional exercise to promote functional recovery and lower limb weight-bearing besides being associated with less postoperative complications.

Key Words: Locking compression plate; T-type steel plate; Complexity; Tibial plateau fracture; Functional recovery; Complications

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i2.502
MATERIALS AND METHODS

Study design
A total of 97 patients with complex tibial plateau fractures who underwent surgery at our hospital were selected for retrospective study. Based on the operation method, 49 patients who were treated with LCP + T-type steel plate limited internal fixation were included in the study group, and 48 patients who were treated with bilateral ordinary steel plate support were included in the control group. The inclusion criteria were as follows: (1) Complex tibial plateau fractures with a clear history of trauma; (2) Closed fracture type; (3) Main clinical symptoms of lower limb pain, swelling, deformity, and dysfunction; (4) Diagnosis of the complex tibial plateau fracture by X-ray and computed tomography; (5) Age 19 to 59 years; (6) Schatzker type V-VI; and (7) Surgery undertaken within 2 wk after the trauma. The exclusion criteria were as follows: (1) Fractures caused by diseases (malignant bone tumor, bone tuberculosis, severe osteoporosis); (2) Presence of hematological diseases; (3) Simultaneous occurrence of severe vascular and nerve injury or soft tissue defects, and a contaminated wound; (4) Mental or intellectual impairment; and (5) Presence of other diseases leading to muscle atrophy or neurological disorders.

Operation method
In the study group, LCP + T-type steel plate limited internal fixation had been performed. The patient was placed half supine, and the affected knee was raised and flexed at approximately 30° with external rotation. A posteromedial incision 8–12 cm in length was made at the posterior edge of the semitendinosus muscle. Entry was at the muscle space between the gastrocnemius muscle and medial head of the semitendinosus muscle. The semi-membranous muscle was cut and pulled medially. The joint capsule was then cut. The medial meniscus was pulled to the femoral side with a meniscus hook to expose the medial and lateral articular surfaces of the tibial plateau. The posteromedial tibial plateau was fixed with a T-shaped plate, and the lateral tibial plateau condyle fracture was treated with a bone graft. After temporary fixation with a Kirschner wire, C-arm fluoroscopy was performed to confirm recovery of the articular surface height. The LCP was selected and adjusted to the best position. A cortical bone screw was temporarily screwed into the appropriate position of the plate, and several locking screws were screwed into the proximal and distal parts of the plate.

In the control group, bilateral ordinary steel plate support was used. The patient was placed semi-supine on the fluoroscopic operating table and an arc incision was made along the adductor tuberosity of the femur, terminating at the medial side of the tibial tuberosity. The skin and subcutaneous tissue were incised to expose the medial expansion of the quadriceps femoris. The sartorius muscle and goose foot were gently pulled back to open the medial joint capsule. At the same time, the meniscus was pulled to the femoral side to clearly expose the medial platform. After fracture reduction, Kirschner wire fixation was used to confirm that the reduction was satisfactory, and an ordinary supporting plate was inserted. After fracture block reduction, an appropriate amount of artificial bone or allogeneic bone was implanted in the bone defect. After confirming that the height of the articular surface was restored, the ordinary supporting plate was selected, and several cancellous lag screws and cortical screws were successively screwed into the proximal and distal parts of the plate.

Observation indices
Operation time, blood loss, anterior external incision length, intraoperative bone graft volume, postoperative drainage volume, hospitalization duration, fracture healing time, complete weight-bearing time, Rasmussen score, tibial plateau varus angle (TPA), tibial plateau retroversion angle (PA), and postoperative complications at different points after surgery in the two groups were assessed and compared.

The Rasmussen score was used to evaluate mainly two aspects the knee joint function: (1) Subjective aspects: degree of pain (6 points) and walking ability (6 points). Based on the findings of physical examination by clinicians, each item of knee stability, knee extension, and range of motion was scored, the highest score being 6; the total scores were classified as excellent (≥ 27), good (20–26), medium (10–19), or poor (< 10); and (2) Radiology: the main outcome measures included condylar widening, articular surface collapse, and angulation deformity, with the highest score of 6 for each evaluation item; the total scores were classified as excellent (18), good (12–17), medium (6–12), or poor (< 6).
The patients were followed up by telephone or by clinic visits for routine examination. The patients were examined and assessed for postoperative complications and knee function recovery. The follow-up duration was at least 18 mo.

**Statistical analysis**

SPSS 21.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Quantitative data such as the operation time and intraoperative bone graft volume were expressed as mean ± SD; t-test was used to analyze the differences between the two groups. Qualitative data, such as the complication rate, were analyzed using the χ² test. P < 0.05 was considered statistically significant.

**RESULTS**

**Patient characteristics**

In the study group, the average age was 38.3 ± 8.5 years (range, 23-55 years). There were 31 males and 18 females. The time interval between the fracture and operation was 7.9 ± 1.2 d. There were 27 fractures on the left side and 22 on the right side. The Schatzker classifications were type V in 22 cases and type VI in 27 cases (Figure 1). The causes of injury were traffic accidents in 31 cases, falls in 11 cases, and other causes in 7 cases.

In the control group, the average age was 40.0 ± 7.2 years (range, 25-56 years). There were 28 males and 20 females. The time interval between the fracture and operation was 8.1 ± 1.1 d. There were 24 cases on the left side and 24 cases on the right side. The Schatzker classifications were type V in 20 cases and type VI in 28 cases. The causes of injury were traffic accidents in 27 cases, falls in 9 cases, and other causes in 12 cases. There was no significant difference in the baseline data between the two groups (P > 0.05).

**Comparison of operation status and postoperative hospital stay between the two groups**

Operation time and intraoperative bone graft volume were lower in the study group than in the control group (P < 0.05). There was no statistically significant difference between the two groups in surgical bleeding, anterior external incision length, postoperative drainage, and duration of hospital stay (P > 0.05) as shown in Table 1.

**Comparison of postoperative fracture healing between the two groups**

Full load bearing was earlier in the study group than in the control group (P < 0.05). There was no statistically significant difference between the study group and the control group in the fracture healing time (P > 0.05, Table 2).

**Comparison of the angles of TPA and PA between the two groups**

There was no statistically significant difference between the two groups in the angles of TPA and PA both immediately after surgery and 18 mo thereafter (P > 0.05, Table 3).

**Comparison of knee joint function between the two groups**

At 12 mo after surgery, the Rasmussen scale subjective evaluation score was significantly higher in the study group than in the control group (P < 0.05). However, there was no significant difference between the two groups in the Rasmussen scale subjective evaluation score at 18 mo after surgery and in the radiology score at 12 and 18 mo after surgery (P > 0.05, Table 4).

**Comparison of surgical complication rates between the two groups**

The postoperative complication rate was significantly lower in the study group than in the control group (3.77% vs 15.09%, P < 0.05) as shown in Table 5.

**DISCUSSION**

The tibial plateau consists of the medial platform, lateral platform, and intercondylar ridge. The bone density of the lateral platform is less than that of the medial platform. When suffering localized trauma, the lateral platform is more prone to split or
Table 1 Comparison of the operation status and length of postoperative hospital stay between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Operation time (min)</th>
<th>Surgical bleeding (mL)</th>
<th>Anterior external incision length (cm)</th>
<th>Intraoperative bone graft (g)</th>
<th>Postoperative drainage (mL)</th>
<th>Hospital stays (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>49</td>
<td>118.3 ± 14.0</td>
<td>339.4 ± 38.0</td>
<td>17.5 ± 2.2</td>
<td>7.10 ± 1.87</td>
<td>139.4 ± 34.0</td>
<td>7.4 ± 1.5</td>
</tr>
<tr>
<td>Control group</td>
<td>48</td>
<td>130.1 ± 16.3</td>
<td>344.1 ± 42.6</td>
<td>17.8 ± 2.6</td>
<td>9.23 ± 2.04</td>
<td>143.8 ± 39.6</td>
<td>7.8 ± 1.7</td>
</tr>
<tr>
<td>t value</td>
<td>-3.827</td>
<td>0.568</td>
<td>-0.614</td>
<td>-5.362</td>
<td>-0.588</td>
<td>-1.229</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>0.541</td>
<td>0.000</td>
<td>0.558</td>
<td>0.222</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Comparison of postoperative fracture healing between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Fracture healing time (wk)</th>
<th>Full load time (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>49</td>
<td>13.5 ± 1.7</td>
<td>14.6 ± 1.2</td>
</tr>
<tr>
<td>Control group</td>
<td>48</td>
<td>14.0 ± 2.0</td>
<td>16.2 ± 1.8</td>
</tr>
<tr>
<td>t value</td>
<td>-1.328</td>
<td>0.187</td>
<td>5.161</td>
</tr>
<tr>
<td>P value</td>
<td>0.187</td>
<td>0.639</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 3 Comparison of the angles of tibial plateau varus angle and tibial plateau retroversion angle between the two groups of patients at different times after surgery (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TPA angle (°)</th>
<th>PA angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Immediately after surgery</td>
<td>18 mo after surgery</td>
</tr>
<tr>
<td>Study group</td>
<td>49</td>
<td>86.34 ± 3.81</td>
<td>86.04 ± 2.51</td>
</tr>
<tr>
<td>Control group</td>
<td>48</td>
<td>86.51 ± 3.44</td>
<td>85.78 ± 2.92</td>
</tr>
<tr>
<td>t value</td>
<td>-0.231</td>
<td>0.639</td>
<td>0.603</td>
</tr>
<tr>
<td>P value</td>
<td>0.818</td>
<td>0.639</td>
<td>0.603</td>
</tr>
</tbody>
</table>

TPA: Tibial plateau varus angle; PA: Tibial plateau retroversion angle.

Table 4 Comparison of knee joint function between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Subjective evaluation score (points)</th>
<th>Radiology evaluation (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>12 mo after operation</td>
<td>18 mo after surgery</td>
</tr>
<tr>
<td>Study group</td>
<td>49</td>
<td>18.84 ± 3.50</td>
<td>25.81 ± 2.50</td>
</tr>
<tr>
<td>Control group</td>
<td>48</td>
<td>16.57 ± 3.32</td>
<td>25.21 ± 2.64</td>
</tr>
<tr>
<td>t value</td>
<td>3.276</td>
<td>0.253</td>
<td>0.534</td>
</tr>
<tr>
<td>P value</td>
<td>0.001</td>
<td>0.253</td>
<td>0.534</td>
</tr>
</tbody>
</table>

collapse. The anterior and posterior cruciate ligaments connect the femoral condyles and tibial intercondylar parts to stabilize the knee joint[5,6]. The medial collateral ligament ends in the marginal compartment of the medial platform; thus, when the medial platform fractures, the medial collateral ligament is prone to contusion or even rupture[7]. Currently, the clinical treatment goal for tibial plateau fracture reduction is anatomical reduction of the articular surface, preventing articular surface collapse or step formation, and firm and stable fixation, so as to obtain a long-term stable, well-aligned, normal, and painless joint, and prevent the occurrence of post-traumatic arthritis and other complications[8]. However, studies have found that complex tibial plateau fractures are often accompanied by other conditions including peripheral ligament injury, surrounding soft tissue swelling, joint instability due to an uneven
Table 5 Comparison of surgical complication rates between the two groups, n (%) 

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Incision infection</th>
<th>Delayed fracture union</th>
<th>Traumatic arthritis</th>
<th>Complication rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>49</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (3.77)</td>
</tr>
<tr>
<td>Control group</td>
<td>48</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>8 (15.09)</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.153</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.042</td>
</tr>
</tbody>
</table>

Figure 1 A 54-year-old male patient suffered a Schatzker type VI fracture on the right side due to a car accident. A-D: The patient received locking compression plate combined with T-plate treatment on day 6 after admission to the hospital. Re-examination of the X-ray results showed that the reduction was good, and the internal fixation was stable; E, F: The results of the re-examination at 18 mo after the operation. The patient's fracture was completely healed.

Surgery is the main treatment modality for complex tibial plateau fractures; to ensure correct reduction and prevention of related complications, it is important to choose the correct operative approach. High-energy injuries can cause Schatzker type V and VI tibial plateau fractures. Most of the knee joint surface becomes severely comminuted and is accompanied by severe soft tissue injury due to intra-articular fractures. The purpose of treating intra-articular fractures is to restore the smoothness of the articular surface, axial alignment, stability of the joint, and normal functional activities of the joint. The treatment chosen at the time of operation must provide enough stability and allow the patient to exercise properly at an early timepoint[10].

In our study, the differences in the outcomes of LCP + T-type steel plate limited internal fixation and bilateral ordinary steel plate support were compared. Bilateral ordinary steel plate operation allows the surgical field to be clearly exposed, thus exposing the joint surface. Through the comprehensive exploration of the articular surface and meniscus ligament injury, the disadvantage of the short distance between the predetermined incision line and the auxiliary incision line in the bilateral incision of the knee can be overcome. However, large soft tissue flaps need to be separated from the medial and lateral sides during the operation, which may cause more injury to patients and require physicians to have higher technical skill[11]. In LCP + T-type steel plate limited internal fixation, an anterolateral conventional incision combined with small posteromedial limited incision can be used to expose each part of the medial and lateral plateau, allowing for the accurate reduction of fracture fragments from different angles and orientations and enabling the management of posterior articular surface, and acute varus[9].
Li HF et al. LCP + T-type steel plate in complex tibial plateau fractures

Studies have found that LCP + T-type steel plate limited internal fixation has the advantages of a smaller contact area with the periosteum, less soft tissue injury, and easier placement of plate. Through biomechanical studies, some scholars have found that the contact area between the ordinary double steel plate and the periosteum is large, which can easily affect the blood supply of the fractured ends after surgery, leading to delayed- or non-union of the fracture after the operation. However, using the medial plate is better because less soft tissue and periosteum removal is required to clearly expose the broken end of the fracture. It not only causes less soft tissue injury but also makes the plate easier to place, which is more conducive for the postoperative recovery of patients[15]. Studies have also found that the use of a medial plate requires a smaller amount of artificial bone or allograft to be inserted to prevent poor support than the traditional double plate; in order to ensure the postoperative reduction of the platform without loss, a large amount of artificial bone or allograft was inserted to support the articular surface height[16-18].

During the operation, we also found that the patient should be in the semi-supine position. By rotating the operating table and the affected limb, the posteromedial and anterolateral parts of the knee could be clearly exposed to facilitate intraoperative fracture reduction. At the same time, the anterolateral and anteromedial incisions can be made simultaneously during the operation to expose the posteromedial side, so that the affected limb is in a slightly flexed state, and the gastrocnemius muscle is relatively relaxed to fully expose the posterior side. In addition, attention should be paid to the protection of the great saphenous vein and saphenous nerve[19,20].

In our study, operation time and intraoperative bone graft volume in the study group was less in the study group than in the control group, indicating that LCP + T-type steel plate limited internal fixation for complex tibial plateau fractures can shorten the operation time and reduce intraoperative bone graft. Full load bearing in the study group was earlier than in the control group, but there was no statistically significant difference in the fracture healing time between the two groups, indicating that LCP + T-type steel plate limited internal fixation for complex tibial plateau fractures is helpful for early training in patients but has no significant effect on the fracture healing time; this finding may have been affected by the small number of patients enrolled. The comparison of TPA and PA angle between the study group and the control group immediately after the operation and at 6 mo after the operation showed no statistically significant differences between the groups, suggesting that the application of the two internal fixation methods in complex tibial plateau fractures will not have an effect on the varus angle and posterior angle. Three months after the operation, the subjective evaluation scores of the Rasmussen scale of the knee in the study group were higher than those in the control group, suggesting that LCP + T-type steel plate limited internal fixation for the treatment of complex tibial plateau fractures is beneficial for the recovery of knee function at the early stage. Furthermore, the rate of postoperative complications was significantly lower in the study group (3.77%) than in the control group (15.09%), suggesting that LCP + T-type steel plate limited internal fixation for the treatment of complex tibial plateau fractures can reduce the incidence of postoperative complications.

This study compared the effects of two internal fixation methods in patients with complex tibial plateau fractures and confirmed that LCP + T-type steel plate limited internal fixation can shorten the operation time and obtain strong and effective internal fixation, which is consistent with the results of previous studies. Meanwhile, this study also found that the LCP + T-type steel plate method has a further advantage of earlier full load bearing, which is conducive for early postoperative knee rehabilitation and exercise; thus, it is more in line with the concept of fracture internal fixation, which was relatively rare in previous studies. However, due to the small number of patients enrolled in this study and many factors affecting the postoperative recovery of patients with complex tibial plateau fractures, long-term follow-up was not carried out in this study. Therefore, it is necessary to expand the sample size, conduct long-term follow-up, and carry out prospective trials for an in-depth demonstration of the superiority of LCP + T-type steel plate limited internal fixation over bilateral ordinary steel plate support in the treatment of complex tibial plateau fractures.

CONCLUSION

In conclusion, LCP + T-type steel plate limited internal fixation treatment has the
advantage of less trauma and enables early postoperative functional exercise to promote functional recovery and lower limb weight-bearing besides being associated with less postoperative complications.

ARTICLE HIGHLIGHTS

Research background
Tibial plateau fracture has a serious impact on the movement and function of the knee joint, resulting in serious dysfunction. The clinical application of locking plate can not only reduce soft tissue injury, but also reduce the occurrence of postoperative necrosis, but the stability of articular surface of locking plate can not be guaranteed. In this study, locking compression plate (LCP) and T-shaped plate were used to treat complex tibial plateau fractures, in order to find a more reliable method of internal fixation for clinic.

Research motivation
This study compared the difference between bilateral common plate support and LCP+ T plate limited internal fixation. Bilateral common plate peeling during operation can make the operative visual field more clearly exposed and expose the articular surface. Through omni-directional exploration of articular surface and ligament meniscus injury, it can further improve the disadvantage of too short distance between predetermined incision line and auxiliary incision line in bilateral incision of knee joint.

Research objectives
This study aimed to explore a surgical method for the treatment of complex tibial plateau fractures with less trauma, faster postoperative recovery and fewer postoperative complications

Research methods
Operation time, blood loss, anterior external incision length, intraoperative bone graft volume, postoperative drainage volume, hospitalization duration, fracture healing time, complete weight-bearing time, Rasmussen score, tibial plateau varus angle, tibial plateau retroversion angle, and postoperative complications at different points after surgery in the two groups were assessed and compared.

Research results
In our study, operation time and intraoperative bone graft volume in the study group was less in the study group than in the control group, indicating that LCP + T-type steel plate limited internal fixation for complex tibial plateau fractures can shorten the operation time and reduce intraoperative bone graft. LCP + T-type steel plate limited internal fixation for the treatment of complex tibial plateau fractures can reduce the incidence of postoperative complications.

Research conclusions
LCP + T-type steel plate limited internal fixation treatment has the advantage of less trauma and enables early postoperative functional exercise to promote functional recovery and lower limb weight-bearing besides being associated with less postoperative complications.

Research perspectives
It is necessary to expand the sample size, conduct long-term follow-up, and carry out prospective trials for an in-depth demonstration of the superiority of LCP + T-type steel plate limited internal fixation over bilateral ordinary steel plate support in the treatment of complex tibial plateau fractures.

REFERENCES
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Li HF et al. LCP + T-type steel plate in complex tibial plateau fractures


Retrospective Study

Effect of Mirena placement on reproductive hormone levels at different time intervals after artificial abortion

Xiao-Xiao Jin, Ling Sun, Xiao-Li Lai, Jie Li, Mei-Li Liang, Xia Ma

ORCID number: Xiao-Xiao Jin 0000-0002-7982-2626; Ling Sun 0000-0001-8813-2507; Xiao-Li Lai 0000-0001-5511-0504; Jie Li 0000-0001-5214-395X; Mei-Li Liang 0000-0001-9023-3008; Xia Ma 0000-0003-4189-3944.

Author contributions: Jin XX and Ma X designed this retrospective study, Jin XX and Sun L wrote this paper; Jin XX, Sun L, Lai XL, Li J, Liang ML and Ma X were responsible for sorting the data.

Institutional review board statement: The study was reviewed and approved by the Zhejiang Taizhou Hospital Institutional Review Board.

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

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

Specialty type: Obstetrics and Gynecology

Provenance and peer review: ORIGINAL ARTICLE

Abstract

BACKGROUND
Improper methods of contraception greatly increase the risk of abortion, cervical or endometrial lesions, and the number of recurrent artificial abortions. These complications result in the deterioration of a patient’s outcome. Further, the proportion of artificial abortions is highest among unmarried females. Placement of an intrauterine device, such as the Mirena, after an artificial abortion may decrease the likelihood of an endometrial injury caused by recurrent abortions while significantly improving its contraceptive effects.

AIM
To discuss the effect of Mirena placement on reproductive hormone levels at different time points after an artificial abortion.

METHODS
Women (n = 119) undergoing an artificial abortion operation were divided into the study (n = 56) and control (n = 63) groups. In the study group, the Mirena was inserted immediately after the artificial abortion, whereas in the control group, it was inserted 4–7 d after the onset of the first menstrual cycle after abortion. All participants were followed-up for 6 mo to observe the continuation and expulsion rates and adverse reactions and to measure the levels of serum estradiol (E2), follicle stimulating hormone (FSH), and luteinizing hormone (LH).

RESULTS
The continuation rates were 94.64% and 93.65% in the study group and the control group, respectively. The expulsion rates were 1.79% and 3.17% in the study group and the control group, respectively. There was no statistically significant difference between the two groups (P > 0.05). There were also no statistically significant differences in the proportion of patients with bacterial vaginitis, trichomonas vaginitis, or cervicitis between the groups (P > 0.05). Six months after Mirena placement, E2 Levels were 45.50 ± 7.13 pg/mL and 42.91 ± 8.10 pg/mL,
A total of 119 women who underwent artificial abortion between January 2017 and
January 2019 were selected. Inclusion criteria were: (1) Pregnancy within 8 wk; (2) Voluntary placement of the Mirena IUD [Bayer HealthCare Pharmaceuticals Co., Ltd Guangzhou Branch, containing levonorgestrel 52 mg/unit (20 µg/24 h)]; (3) Complete clinical follow-up data; and (4) Informed consent from the participant. Exclusion criteria were: (1) Diagnosis of genital malformations, pelvic inflammatory disease, or any sexually transmitted diseases; (2) Association with a malignant tumor, hypertension, diabetes mellitus, immune system diseases, or other basic diseases; and (3) Tissue residue or suspicion thereof after surgery. Participants were divided into either the study group \( (n = 56) \) or control group \( (n = 63) \) according to the time of Mirena placement.

**Treatment methods**
All participants underwent surgical abortions in strict accordance with relevant regulations. Participants in the study group had the Mirena inserted immediately after surgical abortion.

The specific details of the surgery were as follows. All participants were prepared and surgical instruments were disinfected before surgery. The patients underwent a routine gynecological examination using a speculum. After confirmation that none of the exclusion criteria were present, the patients underwent surgery. First, the anterior portion of the cervix was clamped and pulled outward by a cervix clamp. The depth of the uterine cavity was measured using uterine probe along the uterine position, with some participants requiring cervical dilatation. The Mirena IUD was pushed into the patient’s uterus with the placement device. The position of the IUD was checked to ensure accurate placement, and the push rod was removed and disinfected. The external tail wires were cut to retain approximately 1.5 cm of length. The patient was observed for signs of bleeding after removal of the cervical clamp.

The control group had the Mirena placed 4–7 d after the onset of the first menstrual cycle after artificial abortion. Relevant examinations were carried out before surgery to ensure proper procedure. The surgery procedures and methods were the same as in the study group. All participants were prescribed an antibiotics anti-infection treatment after surgery. Sexual intercourse and pelvic baths were prohibited within 7 d and 2 wk after surgery.

**Detection methods**
The following indicators were detected on the 4th–5th day of the menstrual cycle before and after the IUD release in all participants: 5 mL of venous blood samples were collected with limosis, placed for 30 min, and centrifuged at 3000 rpm for 12 min. Serum was collected and LH, FSH, and E2 Levels were determined by electrochemiluminescence using the Beckman Kurt UniCel Dxl 800 chemiluminescence immunoassay analyzer (Zhengzhou Autobio Diagnostics Co., Ltd., Zhengzhou, China) and the EasyBlot ECL chemiluminescence chromogenic reagent (Fisher Scientific, Pittsburgh, PA) according to the manufacturer’s instructions.

The brief index of sexual functioning for women was used to evaluate the quality of each patient’s sexual life, including sexual desire, sexual activity, and sexual satisfaction. The higher the score, the better the quality of sexual life.

**Statistical analysis**
SPSS22.0 software was used for statistical analysis. Independent sample \( t \)-test was used for the comparison of E2, FSH, and LH levels and other indicators between the two groups. \( \chi^2 \) or Fisher’s exact test was used for the comparison of indicators such as the continuation and expulsion rates of the IUD. Test level: Bilateral = 0.05.

**RESULTS**

**Comparison of patient characteristics**
There were no statistically significant differences in age, gravidity, body mass index, and length of menstrual cycles between the two groups \( (P > 0.05) \) (Table 1).

**Comparison of the continuation and expulsion rates of the IUD**
There were no statistically significant differences in the continuation or expulsion rates between the two groups. There were also no statistically significant differences in the proportion of patients with bacterial vaginitis, trichomonas vaginitis, or cervicitis between the study and control groups \( (P > 0.05) \). Moreover, no statistically significant
Table 1 Comparison of general information between the control and study groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Age (yr)</th>
<th>Pregnancy times (Times)</th>
<th>BMI (kg/m²)</th>
<th>Menstrual cycle (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>56</td>
<td>27.84 ± 3.03</td>
<td>2.60 ± 0.45</td>
<td>22.40 ± 3.11</td>
<td>30.21 ± 4.54</td>
</tr>
<tr>
<td>Control group</td>
<td>63</td>
<td>28.15 ± 2.94</td>
<td>2.41 ± 0.58</td>
<td>21.54 ± 4.03</td>
<td>29.62 ± 5.80</td>
</tr>
<tr>
<td>t value</td>
<td></td>
<td>-0.566</td>
<td>1.978</td>
<td>1.291</td>
<td>0.612</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.573</td>
<td>0.050</td>
<td>0.199</td>
<td>0.541</td>
</tr>
</tbody>
</table>

BMI: Body mass index.

difference in the number of women with abnormal menstruation, prolonged menstruation, or pain during intercourse between the groups after IUD placement was observed ($P > 0.05$) (Table 2).

**Comparison of uterine volume, sexual desire, sexual activity, and sexual satisfaction after IUD placement**

There were no statistically significant differences in the E2, FSH, and LH levels between the two groups 6 mo after IUD placement ($P > 0.05$). There was also no statistically significant difference in uterine volume between the two groups before and after IUD placement ($P > 0.05$). There were no statistically significant differences in sexual desire, sexual activity, or sexual satisfaction scores between the two groups after IUD placement ($P > 0.05$) (Table 3).

**DISCUSSION**

The Mirena IUD is a series of birth control rings that interfere with implantation of the fertilized eggs by releasing low levels of progesterone, which affects endometrial receptivity and achieves contraception. Thus far, most clinical practitioners believe that beneficial contraceptive effects from IUD placements are obtained in the month following an artificial abortion[7-9]. However, there are some limitations to IUD placement one month after artificial abortion: (1) The patient requires an additional uterine cavity operation, and repeated uterine orifice expansion increases the risk of endometrial and cervical injuries[10]; and (2) Patients require frequent hospital visits, which can be time-consuming and can affect the work and life of a patient. This study aimed to describe the differences observed between patients who had an IUD placed either immediately following surgical abortion or one month later[11].

Immediate placement of an IUD after surgery prevents repeated operations while reducing a patient’s pain. Further, IUD placement can significantly promote the repair and proliferation of the endometrium and prevent the occurrence of intrauterine adhesions via the release of weak physiological hormones from the IUD[12]. Previous studies have shown that the Mirena can improve contraceptive effects and reduce the risk of intrauterine adhesions compared with other types of IUDs. However, the analysis of the Mirena’s effect on sex hormone levels *in vivo* is insufficient[13].

This study found no significant differences in the continuation or expulsion rates of the IUD at different time points, suggesting that immediate placement of an IUD after surgical abortion does not affect the long-term use of an IUD. Although the uterus is large and the uterine cavity deep, the reasonable use of oxytocin can promote the contraction of the uterus. Based on this, IUD placement can prevent risk from long-term IUD downshift or shedding[14,15].

There was no significant difference in the incidence of vaginitis or cervical lesions between the two groups in our study, indicating that the risk of gynecological infectious diseases is not increased when an IUD is placed immediately after surgical abortion. Immediate IUD placement after artificial abortion does not increase the occurrence of infectious inflammatory diseases on the basis of standard vaginal disinfection under the guidance of aseptic techniques. Other relevant researchers have found that immediate IUD placement after artificial abortion can significantly reduce the risk of long-term vaginitis in patients who undergo abortion and prevent the impact of a secondary IUD placement on the uterine environment[16,17]. The reliability of clinical application is apparent.
Table 2 Comparison of intrauterine device continuation and removal rates, reproductive tract infections, abnormal menstrual volumes, and prolonged menstrual period between the two groups, n (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Observation group (n = 56)</th>
<th>Control group (n = 63)</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuation rate</td>
<td>53 (94.64)</td>
<td>59 (93.65)</td>
<td>0.053</td>
<td>0.818</td>
</tr>
<tr>
<td>Ring removal rate</td>
<td>1 (1.79)</td>
<td>2 (3.17)</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Bacterial vaginitis</td>
<td>6 (10.71)</td>
<td>10 (15.87)</td>
<td>0.678</td>
<td>0.410</td>
</tr>
<tr>
<td>Trichomonal vaginitis</td>
<td>2 (3.57)</td>
<td>3 (4.76)</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Cervicitis</td>
<td>8 (14.29)</td>
<td>11 (17.46)</td>
<td>0.223</td>
<td>0.637</td>
</tr>
<tr>
<td>Abnormal menstrual volume</td>
<td>3 (5.36)</td>
<td>4 (6.35)</td>
<td>-</td>
<td>1.000</td>
</tr>
<tr>
<td>Prolonged menstruation</td>
<td>2 (3.57)</td>
<td>3 (4.76)</td>
<td>-</td>
<td>1.000</td>
</tr>
<tr>
<td>Sexual intercourse pain</td>
<td>1 (1.79)</td>
<td>2 (3.17)</td>
<td>-</td>
<td>1.000</td>
</tr>
</tbody>
</table>

< The use of Fisher’s exact test.

Table 3 Comparison of sex hormone levels, uterine volume, and sex life quality scores between the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Observation group (n = 56)</th>
<th>Control group (n = 63)</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2 (pg/mL)</td>
<td>45.50 ± 7.13</td>
<td>42.91 ± 8.10</td>
<td>1.841</td>
<td>0.068</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>13.60 ± 3.24</td>
<td>14.54 ± 3.11</td>
<td>-1.614</td>
<td>0.109</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>15.11 ± 2.08</td>
<td>14.60 ± 3.55</td>
<td>0.941</td>
<td>0.349</td>
</tr>
<tr>
<td>Uterine volume (cm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before placement</td>
<td>120.33 ± 6.93</td>
<td>119.28 ± 8.03</td>
<td>0.759</td>
<td>0.449</td>
</tr>
<tr>
<td>1 mo after placement</td>
<td>122.10 ± 9.10</td>
<td>121.28 ± 8.28</td>
<td>0.515</td>
<td>0.608</td>
</tr>
<tr>
<td>6 mo after placement</td>
<td>121.15 ± 8.82</td>
<td>122.02 ± 9.11</td>
<td>-0.528</td>
<td>0.599</td>
</tr>
<tr>
<td>Sexual life quality scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual desire (points)</td>
<td>25.68 ± 2.10</td>
<td>25.10 ± 2.81</td>
<td>1.262</td>
<td>0.209</td>
</tr>
<tr>
<td>Sexual activity (points)</td>
<td>38.28 ± 4.48</td>
<td>38.10 ± 5.21</td>
<td>0.201</td>
<td>0.841</td>
</tr>
<tr>
<td>Sexual satisfaction (points)</td>
<td>30.20 ± 3.10</td>
<td>29.82 ± 2.88</td>
<td>0.693</td>
<td>0.49</td>
</tr>
</tbody>
</table>

E2: Estradiol; FSH: follicle stimulating hormone; LH: luteinizing hormone.

E2, FSH, and LH are sexual hormone indicators in patients. We found no significant differences in the levels of E2, FSH, and LH between the control and study groups. This suggests that immediate IUD placement after abortion does not affect the level of sexual hormones, and we also found it does not affect ovarian function after 6 mo. The Mirena’s effects are mostly limited to the local uterine cavity, and it has little effect on the hypothalamus-pituitary-ovarian axis; thus, it does not affect systemic hormone levels. Abnormal menstrual volume, a prolonged menstrual period, and pain during sexual intercourse are common clinical symptoms after IUD placement[18-20]. But we found no statistically significant differences in menstrual volume, the length of the menstrual cycle, or pain experienced during sexual intercourse between the two groups in our study, suggesting that immediate IUD placement after artificial abortion does not increase the occurrence of such adverse reactions. The degree of satisfaction of patients is relatively high. However, this study was conducted in a single center. In the future, we plan to work with other centers to conduct a study with a large sample size.

CONCLUSION

In conclusion, immediate placement of the Mirena IUD after artificial abortion does not increase adverse reactions and prevents secondary surgery to achieve a contraceptive effect.
ARTICLE HIGHLIGHTS

Research background
Placement of an intrauterine device (IUD), such as the Mirena, after an artificial abortion may decrease the likelihood of an endometrial injury caused by recurrent abortions while significantly improving its contraceptive effects.

Research motivation
To discuss the effect of Mirena placement on reproductive hormone levels at different time points after an artificial abortion.

Research objectives
Placement of appropriate IUD after induced abortion can improve the contraceptive effect of patients, reduce adverse reactions caused by contraception, and provide reference for clinical contraceptive treatment.

Research methods
Serum levels of estradiol, follicle-stimulating hormone, luteinizing hormone in patients and the continuation and expulsion rates undergoing different birth control regimens were retrospectively compared.

Research results
The recurrence rates of the two groups were 94.64% and 93.65%, respectively, and there was no significant difference in exclusion rates and adverse reactions. There was no significant difference between the two groups in the proportion of bacterial vaginitis, trichomonas vaginitis, or cervicitis. Six months after Mirena placement, there was no significant difference in hormone levels between the two groups. After the placement of Mirena, there was no significant difference in the proportion of abnormal menstruation, prolonged menstruation and painful intercourse between the study group and the control group. Before and after Mirena placement, there were no significant differences in uterine volume, sexual desire, sexual activity and sexual satisfaction scores between the study group and the control group.

Research conclusions
Placement of a Mirena intrauterine device immediately after an artificial abortion does not increase the risk of adverse reactions and can help prevent endometrial injury caused by recurrent abortions.

Research perspectives
This study took a small number of samples, and the next research direction was to explore the birth control effects of different intrauterine devices.

REFERENCES
Jin XX et al. Mirena placement and reproductive hormone levels after artificial abortion


Diagnostic value of artificial intelligence automatic detection systems for breast BI-RADS 4 nodules

Shu-Yi Lyu, Yan Zhang, Mei-Wu Zhang, Bai-Song Zhang, Li-Bo Gao, Lang-Tao Bai, Jue Wang

Abstract

BACKGROUND
The incidence rate of breast cancer has exceeded that of lung cancer, and it has become the most malignant type of cancer in the world. BI-RADS 4 breast nodules have a wide range of malignant risks and are associated with challenging clinical decision-making.

AIM
To explore the diagnostic value of artificial intelligence (AI) automatic detection systems for BI-RADS 4 breast nodules and to assess whether conventional ultrasound BI-RADS classification with AI automatic detection systems can reduce the probability of BI-RADS 4 biopsy.

METHODS
A total of 107 BI-RADS breast nodules confirmed by pathology were selected between June 2019 and July 2020 at Hwa Mei Hospital, University of Chinese Academy of Sciences. These nodules were classified by ultrasound doctors and the AI-SONIC breast system. The diagnostic values of conventional ultrasound, the AI automatic detection system, conventional ultrasound combined with the AI automatic detection system and adjusted BI-RADS classification diagnosis were compared and analyzed.
be provided.

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

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Core Tip: The accuracy of the AI-SONIC breast system in diagnosing BI-RADS 4 nodules is very high, which can improve the diagnostic accuracy of young doctors. It can also be used to upgrade and downgrade BI-RADS 4 nodules, guide clinical decision-making, reduce the biopsy rate for BI-RADS 4 nodules and prevent the waste of medical resources.

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INTRODUCTION
Breast cancer is the most common malignancy among women worldwide. It is also the leading cause of cancer death in women, seriously threatening health[1]. In January 2021, the American Cancer Society noted in their 2020 global cancer statistics report[2] that the incidence rate of breast cancer has exceeded that of lung cancer, and it has become the type of cancer with the greatest number of malignant tumors worldwide (accounting for 11.7% of the total number of new cases). In addition, the mortality rate of breast cancer (6.9%) ranks fifth among cancers. Ultrasound is an important imaging examination method for breast cancer screening. In 2013, the American Society of Radiology released the fifth edition of the BI-RADS, which added ultrasound content based on the fourth edition and promoted standardized examination of breast ultrasound[3]. However, the malignancy risk of BI-RADS class 4 nodules covers a wide range of 2%–95%, clinical decision-making is challenging, and further puncture biopsy or surgical treatment is often required[4]. Artificial intelligence (AI) automatic detection systems for ultrasound breast cancer screening have attracted the attention of scholars in recent years because of their advantages of rapidity, accuracy and objectivity, providing efficient and accurate support to determine the benign or malignant nature of breast nodules[3]. This study attempted to explore whether an AI automatic detection system helps distinguish benign and malignant BI-RADS 4 breast nodules to reduce the likelihood of biopsy.

RESULTS
Among the 107 breast nodules, 61 were benign (57.01%), and 46 were malignant (42.99%). The pathology results were considered the gold standard; furthermore, the sensitivity, specificity, accuracy, Youden index, and positive and negative predictive values were 84.78%, 67.21%, 74.77%, 0.5199, 66.10% and 85.42% for conventional ultrasound BI-RADS classification diagnosis, 86.96%, 75.41%, 80.37%, 0.6237, 72.73%, and 88.46% for automatic AI detection, 80.43%, 90.16%, 85.98%, 0.7059, 86.05%, and 85.94% for conventional ultrasound BI-RADS classification with automatic AI detection and 93.48%, 67.21%, 78.50%, 0.6069, 68.25%, and 93.18% for adjusted BI-RADS classification, respectively. The biopsy rate, cancer detection rate and malignancy risk were 100%, 42.99% and 0% and 67.29%, 61.11%, and 1.87% before and after BI-RADS adjustment, respectively.

CONCLUSION
Automatic AI detection has high accuracy in determining benign and malignant BI-RADS 4 breast nodules. Conventional ultrasound BI-RADS classification combined with AI automatic detection can reduce the biopsy rate of BI-RADS 4 breast nodules.

Key Words: BI-RADS classification; Artificial intelligence; Breast nodules; Breast tumor
MATERIALS AND METHODS

Study design
From June 2019 to July 2020, 107 breast nodules from 92 patients with BI-RADS class 4 nodules, which were detected by routine ultrasound examination in our hospital and confirmed by pathology through puncture biopsy or operation, were examined. The maximum diameter of the nodules was 0.5-3.7 cm. All the patients were women aged 22-83 (45.1 ± 13.2) years who had undergone routine ultrasound and AI automatic detection system examination before surgery. The exclusion criteria were as follows: patients under the age of 18; patients who were pregnant or lactating; patients with breast prosthesis implantation; or patients with a history of previous breast surgery. The study was approved by the ethics committee of our hospital (ethics approval No. pj-nbey-ky-2019-060-01). All the subjects signed informed consent before the examination.

Ultrasound scanners and AI software
The examination was performed by 2 ultrasound doctors with professional training and 2 years of breast examination experience using a commercially available unit, EPIQ7 (Philips), with a high-frequency linear array probe (5-12 MHz).

Demetics is an AI system based on the deep learning framework De-Light that utilizes ultrasound images for big data analysis of breast nodules. Two convolutional neural networks (CNNs) of large and small sizes were built into the system, and the nodule probability was calculated for each pixel. Then, the separated connected regions were cascaded into a new CNN for 2 classifications. The system has good learning ability and growth after in-depth learning of approximately 50000 breast nodule pathological results. This model automatically identifies two-dimensional grayscale ultrasound images of breast nodules. Radiologists do not need to outline breast nodules. The operator must only import ultrasound images into Demetics, and the system obtains the risk coefficient of the thyroid nodule. The range of the risk coefficient is 0-1, and the cutoff value is set to be 0.5 by the system. If the risk coefficient is ≥ 0.5, the nodule is diagnosed as malignant; if the risk coefficient is < 0.5, the nodule is diagnosed as benign.

Study pipeline
The patient was placed in the supine position, and the upper limbs were raised to fully expose the breast and armpit. Two ultrasound doctors who had received professional training and had 2 years of breast examination experience performed the procedure. After discovering the nodule, they carefully observed it, recorded the boundary, shape and internal echo of the nodule, and classified it according to the BI-RADS classification standard recommended by Zhou et al[6]. In cases of disagreement, the result was determined by negotiation. Irregular shape, vertical growth, boundary hyperechoic halo, irregular edge, microcalcification and posterior echo attenuation were considered malignant indices: if one index was satisfied, the lesion was classified as 4A; if two indices were satisfied, it was classified as 4B; if three indices were satisfied, it was classified as 4C; if four or more indices were satisfied, it was classified as 5. In this study, conventional ultrasound BI-RADS classification defined class 4A nodules as benign and class 4B and 4C nodules as malignant. BI-RADS 4 nodules were selected for detection by an AI automatic detection system.

After routine ultrasound examination, the two doctors used AI automatic detection systems (professional technicians performed AI pre-job training for operators in the early stage). Static ultrasound images that clearly showed breast nodules were transmitted in DICOM format in real time and stored in an automatic sonic breast detection system for automatic labeling, processing and analysis. The breast nodules were automatically quantified and identified through the AI algorithm. According to the malignant characteristics of BI-RADS of the American College of Radiology[4], breast nodules include edge features, structural features, and calcification. The five characteristics of echo type and growth direction can be used to automatically assess benign and malignant nodules, and the probability value of benign and malignant nodules is interpreted by the recording system.

For conventional ultrasound BI-RADS classification with the AI automatic detection system prediction model, malignancy was considered when both indicated malignancies; otherwise, the diagnosis was benign. The prediction model of the AI automatic detection system adjusts the classification of conventional ultrasonic BI-RADS: If the AI score is greater than 0.5, the classification is increased by one category; If the AI score is less than 0.5, the classification is decreased by one category[7].
Statistical analysis
SPSS 21.0 statistical analysis software was used to calculate the sensitivity, specificity, accuracy, Jordan index, positive predictive value and negative predictive value of the conventional ultrasound BI-RADS classification, AI automatic detection system, conventional ultrasound BI-RADS classification with AI automatic detection system and adjusted BI-RADS classification diagnosis; the pathological results were used as the gold standard. The biopsy rate, cancer detection rate and malignancy risk rate of post BI-RADS classification diagnosis were compared with the $\chi^2$ test. In all analyses, a $P$ value below 0.05 was considered significant.

RESULTS

Pathological results
Among the 107 breast nodules, 61 were benign (57.01%), namely, 32 cases of fibroadenoma, 18 of adenopathy, 3 of granulomatous mastitis, 2 of intraductal papilloma, 2 of galactocele, 1 of plasma cell mastitis, 1 of phyllodes tumor, 1 of sclerosing adenosis, and 1 of nodular fasciitis, and 46 were malignant (42.99%), including 31 invasive lobular carcinomas, 4 of invasive ductal carcinomas, 2 of encapsulated papillary carcinoma, 1 of mucinous carcinoma, 1 of undifferentiated carcinoma, 1 of malignant phyllodes tumor and 1 of solid papillary carcinoma (Table 1).

Comparison of the four diagnostic models with pathological results
According to conventional ultrasound BI-RADS classification, 4A nodules were classified as benign, and 4B and 4C nodules were classified as malignant; therefore, 59 malignant and 48 benign nodules were diagnosed. The AI automatic detection system defined 0-0.5 as benign and 0.6-1 as malignant, and 55 malignant and 52 benign nodules were diagnosed (Figure 1 and Figure 2). For conventional ultrasound BI-RADS classification with an AI automatic detection system, the presence of malignancy indices was defined as malignant, and others were defined as benign; therefore, 43 malignant and 64 benign nodules were diagnosed. According to the adjusted BI-RADS classification, if the AI score was greater than 0.5, the classification was upgraded by one category, and if the AI score was less than 0.5, the classification was downgraded by one category; therefore, 63 malignant and 44 benign nodules were diagnosed. BI-RADS classification distribution and risk prediction before and after adjustment were also performed (Table 2).

Diagnostic efficiency of the four diagnostic models
The pathology results were considered the gold standard; furthermore, the sensitivity, specificity, accuracy, Youden index, positive predictive value and negative predictive value of conventional ultrasound BI-RADS classification diagnosis, the AI automatic detection system, the conventional ultrasound BI-RADS classification combined with AI automatic detection system and adjusted BI-RADS classification diagnosis were 84.78%, 67.21%, 74.77%, 0.5199, 66.10% and 85.42%; 86.96%, 75.41%, 80.37%, 0.6237, 72.73%, and 88.46%; 80.43%, 90.16%, 85.98%, 0.7059, 86.05%, and 88.46%; and 93.48%, 67.21%, 78.50%, 0.6069, 68.25%, and 93.18%, respectively (Table 3).

DISCUSSION
The incidence and mortality of breast cancer in China are increasing annually with a growing disease burden. The prevention and treatment of breast cancer are very important[8]. Indeed, early accurate, reliable diagnosis and treatment are crucial for patient prognosis[9,10]. With the screening of breast cancer and attention to health, an increasing number of asymptomatic breast nodules are being identified[11]. According to the National Comprehensive Cancer Network breast cancer clinical practice guidelines[12], BI-RADS 4-type breast nodules should be assessed by biopsy, but only 2% of all breast nodules are positive. Chaiverawattana et al[13] have reported that 92.35% of patients with BI-RADS class 4 breast nodules screened by the guidelines underwent unnecessary biopsies. This issue creates a burden on patients and wastes many medical resources. Although breast ultrasound has the advantages of simple operation, no radiation and low cost, it has large operator dependence and poor repeatability. In fact, there are great differences in ultrasound execution and the
interpretation of images, which results in different BI-RADS classifications. For example, Wang et al[14] reported that among 220 cases of breast nodules, BI-RADS 4A was the dividing point between benign and malignant lesions. After multiple ultrasound examinations, up to 21.8% of cases had two different diagnostic results, which creates confusion among clinicians. This study aimed to find an objective and noninvasive method to determine benign and malignant BI-RADS class 4 nodules by applying an AI automatic detection system.

AI has powerful image analysis and information processing capabilities[15,16] and can mine ultrasonic image information that cannot be captured by human eyes. It can quickly, accurately and objectively analyze images, reduce doctors' burden, alleviate the impact on medical resources, improve the accuracy of diagnosis and help clinicians in prognosis and risk stratification to benefit a majority of patients[17,18]. The AI-SONIC Breast classification technology uses BI-RADS classification as the diagnosis basis, integrates scanning, reading and reporting, and can provide a comprehensive and objective evaluation. The AI-SONIC Breast system has high diagnostic efficiency. In this study, the AI automatic detection systems had higher sensitivity, specificity and accuracy than young doctors but lower diagnostic efficiency than the ultrasonic s-detect classification technology for breast nodules reported by Zhou et al[19]. The reason may be that different AI systems have different degrees of machine training. The nodules selected in this study were BI-RADS 4 and above, excluding some simple and typical benign lesions and increasing the difficulty of diagnosis. The accuracy of the AI-SONIC Breast system with conventional ultrasound BI-RADS classification was 85.98%, which is significantly higher than that of the conventional ultrasound BI-RADS classification (74.77%) and indicates that AI automatic detection has high diagnostic efficiency for BI-RADS class 4 breast nodules, e.g., higher than that of young doctors. Its application in the clinic can improve the diagnostic accuracy of young doctors and increase diagnostic confidence. The system can also be used to upgrade and downgrade BI-RADS class 4 nodules and guide decision-making. The adjusted BI-RADS classification decreased the biopsy rate of breast nodules from 100% to 67.29%, which greatly reduced unnecessary puncture biopsy. The cancer detection rate of BI-RADS classification after adjustment was approximately 61.11%, which was significantly higher than that before adjustment (42.99%); this will help to effectively

### Table 1 results of 107 breast cases

<table>
<thead>
<tr>
<th>Pathological results</th>
<th>Number of nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
<td></td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>32</td>
</tr>
<tr>
<td>Adenosis</td>
<td>18</td>
</tr>
<tr>
<td>Granulomatous mastitis</td>
<td>3</td>
</tr>
<tr>
<td>Intraductal papilloma</td>
<td>2</td>
</tr>
<tr>
<td>Galactocele</td>
<td>2</td>
</tr>
<tr>
<td>Plasma cell mastitis</td>
<td>1</td>
</tr>
<tr>
<td>Phyllodes tumor</td>
<td>1</td>
</tr>
<tr>
<td>Sclerosing adenosis</td>
<td>1</td>
</tr>
<tr>
<td>Nodular fascitis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>31</td>
</tr>
<tr>
<td>Intraductal papillary carcinoma</td>
<td>5</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>4</td>
</tr>
<tr>
<td>Encapsulated papillary carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Malignant phyllodes tumor</td>
<td>1</td>
</tr>
<tr>
<td>Solid papillary carcinoma</td>
<td>1</td>
</tr>
</tbody>
</table>
Lyu SY et al. AI diagnose of BI-RADS 4 nodules

Table 2 Diagnostic efficiency of four diagnostic models

<table>
<thead>
<tr>
<th>Inspection method</th>
<th>Pathology</th>
<th>Benign ($n = 61$)</th>
<th>Malignant ($n = 46$)</th>
<th>Susceptibility (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>Jordan index</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional ultrasound BI-RADS classification</td>
<td></td>
<td></td>
<td></td>
<td>84.78</td>
<td>57.21</td>
<td>74.44</td>
<td>0.5199</td>
<td>61.11</td>
<td>85.42</td>
</tr>
<tr>
<td>Benign ($n = 48$)</td>
<td></td>
<td>41</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant ($n = 59$)</td>
<td></td>
<td>20</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI-SONIC Breast system</td>
<td></td>
<td></td>
<td></td>
<td>86.96</td>
<td>75.41</td>
<td>80.37</td>
<td>0.6237</td>
<td>72.73</td>
<td>88.46</td>
</tr>
<tr>
<td>Benign ($n = 52$)</td>
<td></td>
<td>46</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant ($n = 53$)</td>
<td></td>
<td>15</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI-SONIC Breast system combined BI-RADS classification of conventional ultrasound</td>
<td></td>
<td></td>
<td></td>
<td>80.43</td>
<td>90.16</td>
<td>85.98</td>
<td>0.7059</td>
<td>86.05</td>
<td>85.94</td>
</tr>
<tr>
<td>Benign ($n = 64$)</td>
<td></td>
<td>55</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant ($n = 43$)</td>
<td></td>
<td>6</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted BI-RADS classification</td>
<td></td>
<td></td>
<td></td>
<td>93.48</td>
<td>67.21</td>
<td>78.50</td>
<td>0.6069</td>
<td>68.25</td>
<td>93.18</td>
</tr>
<tr>
<td>Benign ($n = 44$)</td>
<td></td>
<td>41</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant ($n = 63$)</td>
<td></td>
<td>20</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 3 BI-RADS classification distribution and risk prediction before and after adjustment

<table>
<thead>
<tr>
<th>Inspection method</th>
<th>Biopsy rate (%)</th>
<th>Malignancy risk (%)</th>
<th>Cancer detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI-RADS classification before adjustment</td>
<td>100</td>
<td>0</td>
<td>42.99</td>
</tr>
<tr>
<td>4A ($n = 48$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4B ($n = 20$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4C ($n = 39$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted BI-RADS classification</td>
<td>67.29</td>
<td>1.87</td>
<td>61.11</td>
</tr>
<tr>
<td>3 ($n = 35$)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4A ($n = 9$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4B ($n = 20$)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4C ($n = 11$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 ($n = 32$)</td>
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</tbody>
</table>

avoid the waste of medical resources. According to the adjusted BI-RADS classification, the risk of malignancy was approximately 1.87%, and only 2 cases of malignant nodules were downgraded to class 3. One case was mucinous carcinoma, and both conventional ultrasound BI-RADS classification and the AI detection system classified this nodule as benign, i.e., a missed diagnosis. The reason is that breast mucinous carcinoma is a special type of malignant breast tumor with a low incidence rate and is often neglected[20], and its growth is inflated. Sonograms of breast mucinous carcinoma mostly reveal hypoechoic nodules with clear borders and regular morphology, and the posterior echo is enhanced. In general, there is no calcification and no obvious blood flow signal. It has similar sonographic features to benign breast tumors, which are easily misdiagnosed as breast fibroadenoma or adenosis[21]. In our study, this nodule was diagnosed as a BI-RADS 4A nodule by conventional ultrasound. The score of the AI detection system was 0.44, which indicated benign. The other case involved intraductal papillary carcinoma; the nodule was small, and the maximum diameter was only 4 mm. Conventional ultrasound showed that the nodule grew nearly vertically, which was consistent with malignancy, and it was
Lyu SY et al. AI diagnose of BI-RADS 4 nodules

Figure 1 AI-SONIC breast system automatically recognizes markers and quantifies breast nodule characteristics. BI-RADS 4C, breast invasive ductal carcinoma confirmed by pathological findings. A: Conventional ultrasound BI-RADS classification suggests BI-RADS 4C; B: Automatic measurement and display of the growth direction; C: Edge feature analysis: the color changes from blue, green, yellow and red in turn to clear to blur; D: The dotted red line represents a strong echo; E: Based on the longitudinal section of the right breast nodule, the benign and malignancy probability of this lesion was 0.84, as detected by artificial intelligence; F: The pathological diagnosis was invasive ductal carcinoma of the breast.

Figure 2 AI-SONIC breast system automatically recognizes markers and quantifies breast nodule characteristics. BI-RADS 4A, breast fibroadenoma confirmed by pathological findings. A: Conventional ultrasound BI-RADS classification suggests BI-RADS 4A; B: Automatic measurement and display of the growth direction; C: Edge feature analysis: the color changes from blue, green, yellow and red in turn to clear to blur; D: The dotted red line represents a strong echo; E: Based on the longitudinal section of the right breast nodule, the benign and malignancy probability of this lesion was 0.39, as detected by artificial intelligence; F: The pathological diagnosis was fibroadenoma of the breast.

diagnosed as a BI-RADS 4A nodule. The AI detection system suggested 0.38, which was benign. In such cases, a missed diagnosis (or misdiagnosis) can be corrected, and a diagnosis and treatment plan can be decided through short-term follow-up or combined with other new technologies, such as breast contrast-enhanced ultrasound [22], ultrasonic elastography[23], automatic breast volume scanner[24] or puncture biopsy.
The limitations of this article are as follows: (1) The sample size was small, the pathological types were incomplete, and there were no special types of breast cancer, such as neuroendocrine carcinoma, medullary carcinoma and Paget’s disease; (2) Conventional ultrasound was performed by two young doctors, and the diagnostic efficacy of different seniority doctors and AI automatic detection systems was not compared; and (3) The AI-SONIC breast system has certain limitations and cannot recognize and determine dynamic ultrasound images. Its feature analysis does not include important information such as the blood flow signal, peripheral echo and elastic characteristics, and there is a certain error in the judgment of equal echo or small nodules.

CONCLUSION

AI automatic detection has high accuracy in determining benign and malignant BI-RADS 4 breast nodules. Conventional ultrasound BI-RADS classification with AI automatic detection can reduce the biopsy rate of BI-RADS 4 breast nodules.

ARTICLE HIGHLIGHTS

Research background
With the popularization of breast screening, an increasing number of BI-RADS 4 nodules have been detected. According to clinical guidelines, such nodules require biopsy. However, the vast majority of BI-RADS 4 nodules are benign, which results in a large number of unnecessary biopsies.

Research motivation
To reduce the biopsy rate for BI-RADS 4 nodules and prevent the waste of medical resources.

Research objectives
Our goal is to improve the preoperative diagnostic accuracy of breast nodules as much as possible, not only to reduce misdiagnosis and missed diagnosis, but also to avoid unnecessary biopsy.

Research methods
We used an artificial intelligence (AI) system to regrade BI-RADS 4 nodules and used pathology results as the gold standard.

Research results
The diagnostic value of AI detection system is higher than that of other methods. The BI-RADS classification results adjusted by AI detection system are closer to the pathological results.

Research conclusions
The AI system has very high diagnostic efficiency for BI-RADS 4 nodules and can effectively prevent many unnecessary puncture biopsies of such nodules.

Research perspectives
In the future, we will continue to study the application of AI in breast cancer and use AI to predict the prognosis of breast cancer.

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Clinical Trials Study

Analysis of 20 patients with laparoscopic extended right colectomy

Hui-Da Zheng, Jian-Hua Xu, Yu-Rong Liu, Ya-Feng Sun

ORCID number: Hui-Da Zheng 0000-0002-4986-8770; Jian-Hua Xu 0000-0001-5147-292X; Yu-Rong Liu 0000-0001-7280-1745; Ya-Feng Sun 0000-0002-0454-123X.

Author contributions: Zheng HD, Xu JH contributed equally to this study and should be regarded as co-first authors; Zheng HD and Xu JH designed the study, collected the data and performed the analysis; Zheng HD, Sun YF and Liu YR wrote the manuscript; Sun YF and Xu JH provided clinical advice, reviewed the manuscript and gave final approval of the version of the article to be published.

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

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

Abstract

BACKGROUND
Currently, the standard surgical procedure for right colon cancer is complete mesocolic excision. Whether preventive extended lymph node dissection for colon cancer located in the hepatic flexure or right transverse colon should be performed remains controversial because the safety and effectiveness of the operation have not been proven, and infrapyloric lymph nodes (No. 206) and lymph nodes in the greater curvature of the stomach (No. 204) have not been strictly defined and distinguished as surgical indicators in previous studies.

AIM
To analyze the metastatic status of infrapyloric lymph nodes and lymph nodes of the greater curvature of the stomach and perioperative complications and systematically evaluate the feasibility and safety of laparoscopic extended right colectomy using prospective data collected retrospectively.

METHODS
The study was a clinical study. Twenty patients with colon cancer who underwent laparoscopic extended right colon resection in our hospital from June 2020 to May 2021 were included.

RESULTS
Among the patients who underwent extended right colon resection, there were no intraoperative complications or conversion to laparotomy; 2 patients had gastrocolic ligament lymph node metastasis, and 5 patients had postoperative complications. The patients with postoperative complications received conservative treatment.

CONCLUSION
Laparoscopic extended right colon resection is safe. However, malignant tumors located in the liver flexure or the right-side transverse colon are more likely to
INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related death[1]. Studies have shown that the survival rate of patients with right colon cancer is significantly lower than that of patients with colorectal malignancies in other locations[2]. Most colorectal surgeons consider complete mesocolic excision (CME) the standard surgery for right-side colon cancer, and CME can improve the long-term survival rate of patients. The principles are as follows: (1) Accurate dissection of the Toldt space and preservation of the colonic membrane; (2) Ligation of the root vessels; and (3) Extended lymph node dissection in tumors located in the liver curve and right half of the transverse colon[3,4]. So-called extended lymph node dissection refers to the removal of the infrapyloric lymph nodes and greater curvature lymph nodes that are 10 cm to 15 cm from the tumor[5]. In 1995, Toyota et al.[6] found that 5 cases (2%) of colonic hepatic flexure cancer had infrapyloric lymph node metastasis and advocated that if lymph node metastasis is suspected, the infrapyloric lymph node should be removed. Feng et al[7] showed that the infrapyloric lymph node metastasis rate in colonic hepatic flexure cancer was 9.1%, and the greater gastric curvature lymph node metastasis rate was 7.1%. Near colonic hepatic flexure cancer has the possibility of metastasis to the infrapyloric and greater curvature lymph nodes. Few studies concerning the metastasis of the gastrocolic ligament (infrapyloric lymph nodes and greater curvature lymph nodes) in liver flexure and right-side transverse colon adenocarcinoma have been conducted, and these studies were retrospective with small sample sizes. Most extended operations did not sweep the infrapyloric lymph nodes, resulting in great heterogeneity at baseline. We aimed to analyze the metastasis of gastrocolic ligament lymph nodes and perioperative complications to evaluate the feasibility and safety of laparoscopic extended right colectomy.

MATERIALS AND METHODS

Patients

This prospective study included 20 patients who underwent laparoscopic extended right colectomy at the Gastrointestinal Surgery Department of The Second Affiliated Hospital of Fujian Medical University from June 2020 to May 2021. The study was prepared and revised according to the CONSORT 2010 statement.
approved by the Ethics Committee of The Second Affiliated Hospital of Fujian Medical University.

The inclusion criteria were as follows: (1) Patients aged ≥ 18 years or ≤ 75 years; (2) An ASA score of I-III; (3) Colon adenocarcinoma or high-grade intraepithelial neoplasia pathologically confirmed by preoperative colonoscopy biopsy; (4) A tumor located on the near liver flexure of the colon or the right 1/3 of the transverse colon; (5) The surgical method of extended right hemicolectomy (CME); (6) A preoperative staging assessment using cT2-4aN0M0 or cTanyN+M0; and (7) Elective surgery. The exclusion criteria were as follows: (1) A number of lesions greater than 2; (2) Preoperative staging of cT1N0 or cT4bNany; (3) Distant metastasis or tumor invading the surrounding tissues; (4) History of malignant tumors or history of major abdominal surgery; and (5) Emergency surgery. All operations were performed by the same surgeon, who performed over 3000 Laparoscopic colorectal surgeries.

Surgical techniques

All operations were performed by the same colorectal surgeon, who has experience with 3000 cases of gastrointestinal tumor surgery. The intestinal segment was removed on the basis of CME[8]. We strictly defined the scope of lymph node dissection in No. 204 and No. 206 as follows: No. 206 was defined as lymph nodes in the area surrounding the root of the right gastroepiploic artery (up to its first branch and down to the junction of the right gastroepiploic vein and superior anterior pancreaticoduodenal vein), No. 204 was defined as lymph nodes distributed along the greater curvature of the stomach distal to the first branch of the right gastroepiploic artery. Each patient was placed in the supine position. The five-hole method was used (Figure 1A). (1) The surgical approach was the caudal ventral approach (Figure 1B); (2) The D3 lymph node tissue dissection method was as follows: centered on the left edge of the superior mesenteric artery (SMA) and separated toward the pancreatic neck; the SMA branch was first cut, and then, the superior mesenteric vein (SMV) branch was cut. This approach does not easily damage the SMA branch across the SMV or cause bleeding. Notably, the middle colonic artery had to be ligated and cut at the root (Figure 1C); (3) Radical resection of expanded right colon cancer requires sweeping the lymphatic tissue on the gastro-omental arch 10 cm from the cancer, including infrapyloric lymph nodes (No. 206) and greater curvature lymph nodes (No. 204) (Figure 1D). Care should be taken when separating the infrapyloric blood vessels, which easily causes bleeding and the rapid formation of hematomas, and it can be difficult to find the bleeding points; (4) Intestinal resection and anastomosis were performed as follows: we used an auxiliary incision to remove the intestine, cut along the precut line to remove the specimen, and performed an end-to-side anastomosis of the distal ileum and the distal transverse colon (Figure 1E); and (5) The skin was sutured.

Pathologic procedures

After the specimen was obtained, an attending physician with rich clinical experience cut the lymph node tissue according to the distribution of the blood vessels, including the lymph nodes at the beginning of the ileocolonic artery, right colon artery, and middle colon artery, and separated the No. 206 and No. 204 lymph nodes for the pathological examination.

Postoperative complications

The complications were described in accordance with the Clavien-Dindo classification [9]. The postoperative complications of the patients were recorded in detail.

RESULTS

The study lasted 11 mo and included 20 patients who strictly met the inclusion criteria. The entire operation process was performed smoothly in 20 patients, and there were no intraoperative conversions to laparotomy or serious intraoperative complications. The median age was 63.5 years (range, 26-75 years), and only one patient was younger than 40 years. The median intraoperative blood loss was 50 mL (range, 20-300 mL). The median operative time in our study was 150 min (range, 170-389 min). The median postoperative anal exhaust time was 3 d (range, 2-6 d). The median time to eat semiliquid food after surgery was 5 d (range, 4-7 d). The median length of hospital stay after surgery was 11.5 d (range, 8-24 d). One case (5%), 16 cases (80%), 3 cases (15%), 9 cases (45%), 7 cases (35%), and 4 cases (20%) had postoperative pathological
Figure 1 Surgery process photos. A: Five-hole method and main operation hole (black arrow); B: Caudal ventral approach in which the assistant lifts the ileocolonic vascular pedicle, and an ultrasonic knife is inserted obliquely in the direction of the superior mesenteric vein (SMV) (dotted line) into the small intestine ascending colon space; C: SMV with broken branches and Henle trunk (white arrow); D: Dissection of gastrocolic ligament lymph nodes; E) Postoperative specimens.

In total, 5 (25%) patients had postoperative complications, including 2 cases of delayed gastric emptying (gastroparesis), 2 cases of intestinal obstruction, 1 case of postoperative gastrointestinal bleeding, 1 case of wound infection, 1 case of pancreatic fistula, and 1 case of chylous ascites. One patient had three complications (wound infection, intestinal obstruction, and pancreatic fistula). All patients were cured by conservative treatment. The details are shown in Table 2.

The number of lymph nodes retrieved and metastases found are shown in Table 2. In total, 11 (55%) patients had lymph node metastasis, and 8 (40%) patients had apical lymph node metastases. The mean ± SD of the number of lymph nodes dissected was 39.3 ± 10.9 nodes, and the median number of metastatic lymph nodes was 1 node (range, 0-28 nodes). The median number of No. 204 lymph nodes was 2 (range, 0-8 nodes), and the median number of No. 206 lymph nodes was 2.5 (range, 0-9 nodes); only 1 patient had lymph node metastasis of No. 206, and 1 patient had lymph node metastasis of No. 204. The details are shown in Table 3.

The detailed information of the patients with No. 204 lymph node or No. 206 lymph node metastasis is shown in Table 4. We found the following pattern: The patients with No. 204 lymph node or No. 206 lymph node metastasis generally had late T and N staging, and apical lymph nodes often had metastases. Moreover, cancer cells can usually be found in the vasculature or nerve tissue, affecting the survival time of patients.
Table 1 Patient demographics and pathological characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>63.5 (26–75)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>BMI (&gt; 25)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>ASA ≤ 2</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
</tr>
<tr>
<td>Hepatic flexure</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Right transverse</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>pT1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>pT2</td>
<td>1 (5)</td>
</tr>
<tr>
<td>pT3</td>
<td>16 (80)</td>
</tr>
<tr>
<td>pT4</td>
<td>3 (15)</td>
</tr>
<tr>
<td>pN0</td>
<td>9 (45)</td>
</tr>
<tr>
<td>pN1</td>
<td>7 (35)</td>
</tr>
<tr>
<td>pN2</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Defective mismatch repair</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Intraoperative complications</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Transition to open abdomen</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

CEA: Carcinoembryonic antigen; ASA: American Society of Anesthesiologists.

DISCUSSION

CME is currently recognized as a surgical method for right-side colon cancer that can improve lymph node collection and the length of surgical specimens without increasing intraoperative and postoperative complications[9]. Compared with left-side colon carcinoma and rectal carcinoma, the prognosis of right-side colon cancer is worse, which may be the result of inadequate tumor and lymph node resection, especially in the liver flexure and right transverse colon. Tumors often appear as No. 204 and No. 206 lymph node metastases if the lymph node is not cleared, which may increase the possibility of tumor recurrence and reduce the survival rate of patients with right colon cancer[2,4]. Although our study has a small sample size, the inclusion criteria are strict, and currently, similar prospective studies are lacking; thus, this study can provide a good reference for clinicians.

Laparoscopic extended right colectomy is one of the most challenging operations in colorectal surgery due to the difficulty in determining the origin of the middle colon artery because of the complex anatomy near the pancreatic neck[11]. The correct identification and cutting of the middle colon artery and careful separation of the inferior pylorus vessels are critical for the safe implementation of laparoscopic extended right hemicolectomy, representing a serious challenge for surgeons[12]. Therefore, the safety of laparoscopic extended right hemicolectomy is still controversial, but most studies suggest that the procedure is safe and feasible. Zhao et al[13] considered that laparoscopic extended right hemicolectomy was a technically feasible and safe surgical method and could obtain the same short-term oncological results as open surgery. In their study, 9 cases (9/220, 4.1%) were converted to open abdomen, 4 cases (4/9, 44.4%) were T4a, and two cases (2/9, 22.2%) had massive bleeding during the process of stripping the right gastrocnemic artery root, which is less than 14% to 19% of the other randomized control study[14,15]. However, the above study did not clarify the lymph node metastasis incidence of No. 204 and No. 206 and only focused...
### Table 2 Peri- and postoperative patient outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative complication</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pancreatic fistula POPF grade</td>
<td></td>
</tr>
<tr>
<td>Grade A</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade B</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Grade C</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Chylous ascites</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Incision infection</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Gastroparesis</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Organ infection</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Clavien–Dindo classification</td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Grade II</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Grade III and above</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Anal exhaust time, median (range) (d)</td>
<td>3 (2-6)</td>
</tr>
<tr>
<td>Semiliquid diet, median (range) (d)</td>
<td>5 (4-7)</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>11.5 (8-24)</td>
</tr>
</tbody>
</table>

POPF: Postoperative pancreatic fistula.

### Table 3 Lymph node yield and metastases

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total LN yield, mean ± SD</td>
<td>39.3 ± 10.9</td>
</tr>
<tr>
<td>LN metastases, median (range)</td>
<td>1 (0-28)</td>
</tr>
<tr>
<td>No. 204 LN yield, median (range)</td>
<td>2 (0-8)</td>
</tr>
<tr>
<td>No. 206 LN yield, median (range)</td>
<td>2.5 (0-9)</td>
</tr>
<tr>
<td>Apical LN metastases</td>
<td>8 (40)</td>
</tr>
<tr>
<td>No. 204 LN metastases</td>
<td>1 (5)</td>
</tr>
<tr>
<td>No. 206 LN metastases</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

LN: Lymph node.

We observed some characteristics of the postoperative complications in our study. The incidence rate of gastroparesis was 10% in the present study, which is significantly higher than that of right colectomy without clearing the lymph nodes of the gastrocolic ligament (10% vs 0.3%)[16]. It is generally believed that 30%-50% may cause gastroparesis in diabetic patients. However, our patients with gastroparesis had normal blood sugar[17]. We considered that the occurrence of gastroparesis was related to the patients who underwent gastrocolic lymph node dissection. Therefore, additional research is needed to determine the best surgical indications and avoid unnecessary and futile gastrocolic ligament lymph node dissection in the future. Few studies examined the causes of gastroparesis after extended right hemicolectomy. We suggest...
that the ultrasound knife burns the stomach during the removal of the omental blood vessels, resulting in decreased gastric motility. You et al.\textsuperscript{[18]} suggested that preserving the right gastroepiploic vessels can reduce the incidence of gastroparesis; however, in this case, No. 206 lymph nodes cannot be completely cleared. According to our clinical experience, when dissociating from the arch, we should cut the blood vessels 0.5 cm away from the great curvature of the stomach when dissociating on the arch to avoid burning the stomach and causing gastroparesis. The other complications seem to be related to colectomy rather than gastrocolic ligament resection. Some authors\textsuperscript{[4]} observed gastric perforation after extended right hemicolectomy, which may be related to gastrocolic ligament resection, and some patients had a dissecting thoracic aorta aneurysm, which may be due to an impaired blood supply to the main abdominal cavity. In our study, there were no intraoperative complications or conversion to laparotomy. The reasons may be that this study had a small sample because the inclusion criteria were strict and the operation was performed by the same gastrointestinal oncologist with extensive laparoscopic experience. In conclusion, we believe that laparoscopic extended right colectomy is safe but should be performed by skilled surgeons.

The probability of metastasis of gastrocolic ligament lymph nodes was 10% in our study. This result is similar to previous studies showing that the probability of lymph node metastasis of the gastrocolic ligament is relatively low. We found that the probability of lymph node metastasis of the gastrocolic ligament with tumors located in the hepatic flexure or right-side transverse colon is significantly higher than that of gastrocolic ligament lymph node metastasis.

### Table 4 Characteristics of the patients with gastrocolic ligament lymph node metastasis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>69</td>
<td>61</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>BMI</td>
<td>30.04</td>
<td>20.96</td>
</tr>
<tr>
<td>Symptom</td>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>CEA (ng/mL)</td>
<td>33.28</td>
<td>25.39</td>
</tr>
<tr>
<td>ASA score</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Location</td>
<td>R</td>
<td>H</td>
</tr>
<tr>
<td>Pathological type</td>
<td>Ulcerative</td>
<td>Ulcerative</td>
</tr>
<tr>
<td>Differentiation</td>
<td>M</td>
<td>m-p</td>
</tr>
<tr>
<td>T stage</td>
<td>T4a</td>
<td>T3</td>
</tr>
<tr>
<td>N stage</td>
<td>N2</td>
<td>N2</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>6.0 × 3.5</td>
<td>6.0 × 5.5</td>
</tr>
<tr>
<td>Mesocolic LN metastases/mesocolic LN yield (n)</td>
<td>5/34</td>
<td>28/58</td>
</tr>
<tr>
<td>Apical LN metastases/apical LN yield (n)</td>
<td>4/13</td>
<td>16/30</td>
</tr>
<tr>
<td>No. 204 LN metastases/GCLN yield (n)</td>
<td>1/2</td>
<td>0/2</td>
</tr>
<tr>
<td>No. 206 LN metastases/GCLN yield (n)</td>
<td>0/6</td>
<td>3/3</td>
</tr>
<tr>
<td>Venous invasion (n)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Perineural invasion (n)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mismatch repair protein</td>
<td>Expression</td>
<td>Expression</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Chemotherapy method</td>
<td>XELOX</td>
<td>XELOX</td>
</tr>
<tr>
<td>Relapse</td>
<td>No</td>
<td>Metastasis</td>
</tr>
<tr>
<td>Mortality</td>
<td>Alive</td>
<td>Death</td>
</tr>
</tbody>
</table>

CEA: Carcinoembryonic antigen; ASA: American Society of Anesthesiologists; CEA: Carcinoembryonic antigen; ASA: American Society of Anesthesiologists; GCLN: Gastrocolic ligament lymph node; R: Right transverse; T: Hepatic flexure; m-p: moderately differentiated-poorly differentiated; XELOX: Oxaliplatin combined with capecitabine.
Colon cancer in other locations. Therefore, tumors located in high-risk locations should undergo extended right hemicolectomy combined with infrapyloric and greater curvature lymph node dissection\(^6\). The main risk factors for gastrocolic ligament lymph node metastasis in right colon cancer are nerve invasion, pN2 stage, carcinoembryonic antigen, poor differentiation and apical lymph node metastasis\(^4,\,16\). We can further confirm this conclusion given the data shown in Table 4. These factors are high-risk and lead to a poor prognosis in colon cancer patients, indicating that the occurrence of gastrocolic ligament lymph node metastasis is closely related to the patient survival rate.

Whether lymph node metastasis of the gastrocolic ligament is regional lymph node metastasis or distant metastasis remains controversial\(^4,\,19\). Based on the limited available data, it is difficult to draw a conclusion. However, this does not affect the need for postoperative chemotherapy in some patients. Twelve patients received regular adjuvant chemotherapy, oxaliplatin combined with capecitabine. One patient died of liver metastasis and pulmonary infection 7 mo after the operation. The TNM stage of the patient was T3N2M0, with lymph node metastasis of the gastrocolic ligament and vascular and nerve invasion, indicating a poor prognosis. The remaining patients had no recurrence or metastasis during the follow-up. Notably, Saluja et al\(^20\) showed that there was no significant difference in survival between young patients and elderly patients. To date, few studies conducted a survival analysis of patients with laparoscopic extended right colectomy. The short-term efficacy and long-term prognosis still require further investigation.

This study demonstrated the rate of gastrocolic ligament lymph nodes located in the liver flexure or the right transverse colon and comprehensively evaluated the safety, feasibility, and short-term efficacy of lymph node dissection in this area, providing important clinical significance; however, there are still several limitations. First, this article reports a single-center analysis based on a clinical study. The inclusion and exclusion criteria were strict, and the length of time was short, resulting in a small sample size, which cannot reach the sample size required for calculation. Second, due to the current short follow-up time, the long-term prognosis of the patients cannot be assessed. A multicenter clinical study investigating this subject in the future is expected to further confirm the results we discussed and evaluate the long-term prognosis of patients.

**CONCLUSION**

Malignant tumors located in the hepatic flexure or right transverse colon have the possibility of gastrocolic ligament lymph node metastasis, and there are indications for laparoscopic extended right colectomy. The surgical approach is safe but could notably increase the incidence of gastroparesis. However, the prognostic effect still needs further analysis.

**ARTICLE HIGHLIGHTS**

**Research background**

Whether laparoscopic extended right colectomy is necessary for colon cancer with tumor located in hepatic flexure and right transverse colon is still controversial.

**Research motivation**

It is of great concern whether laparoscopic extended right colectomy is necessary for tumors located in the hepatic flexure and the right transverse colon. Currently, there is an urgent need to understand the law of lymph nodes of the gastrocolic ligament and the safety of the operation.

**Research objectives**

This study aimed to study the necessity and safety of laparoscopic extended right colectomy.

**Research methods**

This is a clinical study of 20 patients who underwent laparoscopic extended right colectomy. This article describes the surgical technique of laparoscopic extended right
Patients with laparoscopic extended right colectomy and the perioperative information of patients.

**Research results**
There were no intraoperative complications and conversion to laparotomy in 20 patients. Lymph node metastasis of gastrocolic ligament occurred in 10% of patients, and postoperative complications occurred in 5 patients.

**Research conclusions**
Laparoscopic extended right colectomy is safe, but it may significantly increase the risk of postoperative gastroparesis.

**Research perspectives**
This study is expected to increase the sample size and follow-up time.

**REFERENCES**


Observational Study

Knowledge, attitude, practice and factors that influence the awareness of college students with regards to breast cancer

Qiao-Ni Zhang, Hui-Xia Lu

ORCID number: Qiao-Ni Zhang 0000-0001-9980-580X; Hui-Xia Lu 0000-0002-1244-4587.

Author contributions: Zhang QN contributed to the project development. Data collection and manuscript writing; Lu HX contributed to the manuscript revision; all authors reviewed the manuscript.

Institutional review board statement: All subjects provided informed consent and participated voluntarily. This study was approved by the Ethics Committee of the first affiliated hospital of Dali University (No. DFY20200712).

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.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at haohao021021@foxmail.com.

STROBE statement: The authors have read the STROBE.

Abstract

BACKGROUND
Breast cancer has the highest incidence of all global cancers. Recent data show that breast cancer is becoming more prevalent in the younger population. Therefore, preventing breast cancer in young populations is a significant priority for public health. Relevant investigations of the incidence of breast cancer in young females have already been undertaken in China; however, none of these previous studies investigated the awareness of female college students with regards to breast cancer.

AIM
To investigate the knowledge, attitude, and practice (KAP) of female college students in Yunnan with regards to breast cancer and a series of influential factors.

METHODS
A random sample of 1387 female college students from two universities in Dali city were investigated by questionnaires.

RESULTS
The total KAP scores for breast cancer were 9.86 ± 2.50, 3.19 ± 2.01 and 13.31 ± 2.49, respectively. Multiple linear regression analysis showed that educational grade was the most significant influential factor underlying the level of knowledge female college students had with regards to the treatment of breast cancer ($P < 0.05$). Registered residence and educational grade were the most significant factors that influenced attitude ($P < 0.05$). Age, registered residence, grade and major, were the most significant factors that influenced behavior ($P < 0.05$). The KAP of female college students in western Yunnan with regards to...
INTRODUCTION

In 2020, 2.26 million new cases of female breast cancer were diagnosed; consequently, breast cancer replaced lung cancer and became the most common form of cancer in the world. The early onset of breast cancer can be indicative of a familial case of breast cancer. According to the annual report of China cancer residence in 2017, there are 210,000 new cases of breast cancer in China each year, with an annual growth rate of 2% [1]. By 2020, there were 420,000 new cases; furthermore, data showed that patients were younger [2-5]. The screening guidelines for breast cancer recommended by the American Cancer Society indicate that the incidence rate of breast cancer is higher among women aged 20-39 years, and that the preventing the occurrence of breast cancer in younger age groups should be the key focus for the formulation of public health policies [6,7].

The knowledge, attitude, and practice (KAP) of young women is very important if we are to reduce the morbidity and mortality associated with breast cancer. If we can reduce the trend for breast cancer by primary prevention in the younger groups, then it will be possible to reduce the incidence rate significantly over the next 30 years [3-5]. China has already carried out a survey on young women with regards to understanding breast cancer and self-examination [6]. Research studies have also been published that describe regional differences and ethnic characteristics with regards to breast cancer awareness [5-11]. However, many female college students are not aware of breast cancer, thus resulting in a lower self-examination rate; this is because they do not feel that breast cancer is likely to affect them.

Yunnan is in the western borderland of China; this area is associated with more minorities and poorer medical conditions. Public health care should be provided first to college students, who would be the main force behind the transmission of health knowledge and behavior. However, the KAP of female college students about breast cancer in Yunnan was unknow. In this study, we aimed to investigate the KAP of female college students in Yunnan of breast cancer and investigate associated influential factors. Our findings should provide an appropriate foundation for the development of effective health education programs for young women in China with regard to breast cancer.

Key Words: breast cancer; Regression analysis; Rejuvenation; Western Yunnan; College students; Knowledge, attitude and practice

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Country/Territory of origin: China

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report’s scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

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Core Tip: By applying self-designed questionnaires that specifically targeted the knowledge, attitude, and practice of college students at two universities, we were able to ascertain that the knowledge levels of college students in Yunnan with regards to breast cancer were low. Collectively, our data indicated that we should strengthen publicity and educational strategies on university campuses with regards to breast cancer, particularly in terms of prevention, self-examination and examination methods. These strategies will reduce the incidence of breast cancer, specifically in the younger population.
MATERIALS AND METHODS

Participants
Between October 2020 and February 2021, we randomly selected 1346 female college students from two university campuses in western Yunnan, including those studying different majors (medicine, non-medical science, non-medical arts) and those achieving different grades. All subjects provided informed consent and participated voluntarily. This study was approved by the Ethics Committee of the First Affiliated Hospital of Dali University (No. DFY20200712).

Research methods
Design of the questionnaire: Promoting our questionnaire included 5 items of basic information (age, nationality, registered residence, grade and major), 16 items related to preventative behaviors (including time, method, and motivation for breast self-examination), and eight items relating to the basic knowledge of breast cancer according to the KAP. "No", "Uncertain" and "Yes" were allocated scores of 0-2; "Oppose", "Uncertain", "Understand" and "Agree" were allocated scores of 0-3. The total score for the knowledge dimension (question numbers 1-2; question numbers 4-11) ranged from 0-20; the total scores for the attitude dimension (question numbers 14-18) ranged from 0-10; and the total scores for the practice dimension (question numbers 3, 12-13, and 19-20) ranged from 3-19. Forms were completed anonymously by the participants and then analyzed.

The content validity of the questionnaire was 0.780, the total Cronbach's alpha coefficient was 0.702, and the Cronbach's alpha coefficients for each dimension were 0.533, 0.697, and 0.563.

Quality control
The returned questionnaire was first coded and verified. Those that were missing > 10% of data were invalid. In total, 1390 questionnaire were sent out to students and 1346 valid questionnaire were returned. This represented an effective recovery rate of 96.83%.

Statistical analysis
Solutions SPSS version 25.0 software (IBM, Armonk, N.Y., United States) was used for real-time data entry and statistical analysis. A histogram was used to test the normality of raw data. Data were then described as means, standard deviations, standard errors, frequencies, and percentages. Statistical comparisons were carried out with the t-test and one-way analysis of variance. Multivariate linear regression analysis was also performed. Tests were two-way and P < 0.05 was statistically significant.

RESULTS

KAP scores for breast cancer in college students
The full marks of the three dimensions were different, in order to increase the reliability of the conclusion, the full marks for each dimension were standardized to 100 and then compared with the standardized mean. The scores for knowledge and practice for breast cancer in female college students in western Yunnan were significantly higher than the score for attitude (P < 0.05). As the age of the college students increased, the three items that make up the KAP score also increased significantly (P < 0.05). We also identified significant differences in the KAP scores when compared between students of different nationalities (P > 0.05). The KAP scores of senior students were significantly higher than those of junior students (P < 0.05). The scores for attitude and practice for urban students were significantly higher than those of rural students (P < 0.05); there was no significant difference with regards to knowledge score (P > 0.05). However, there was significant difference in terms of the attitude and practice scores between students with different majors (P < 0.05), although there were no significant differences in the knowledge scores (P > 0.05) (Tables 1 and 2).

An analysis of factors that influence KAP scores for breast cancer
When taking age as the measurement data and using multiple linear regression analysis, we found that the knowledge score could be predicted by the student’s grade
(P < 0.05) with a regression coefficient of 0.635. We also found that attitude score could be predicted according to the student’s registered residence and grade (P < 0.05) with regression coefficients of -0.542 and 0.448 respectively. Practice score could be predicted according to the student’s age, registered residence, grade and major (P < 0.05); the regression coefficients were 0.156, -0.691, 0.522, and -0.217, respectively (Table 3).

When taking age as the ranked data and using multiple linear regression analysis, we found that knowledge score could be predicted according to the student’s grade (P < 0.05); the regression coefficient was 0.704. We also found that attitude score could be predicted according to the student’s registered residence and grade (P < 0.05); the regression coefficients were -0.542 and 0.473, respectively. Practice score could be predicted according to the student’s registered residence, grade and major (P < 0.05); the regression coefficients were -0.677, 0.583, and -0.193, respectively (Table 4).

### Table 1 Knowledge, attitude, and practice scores for 1346 female college students with regards to breast cancer (n = 1346, mean ± SD)

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Score</th>
<th>Lowest score</th>
<th>Highest score</th>
<th>Score</th>
<th>Standard score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td>0-20</td>
<td>0</td>
<td>20</td>
<td>9.86 ± 2.50</td>
<td>49.28 ± 12.48</td>
</tr>
<tr>
<td>Attitude</td>
<td>0-10</td>
<td>0</td>
<td>10</td>
<td>3.19 ± 2.01</td>
<td>31.95 ± 20.08</td>
</tr>
<tr>
<td>Practice</td>
<td>3-19</td>
<td>3</td>
<td>19</td>
<td>13.31 ± 2.49</td>
<td>63.36 ± 11.86</td>
</tr>
</tbody>
</table>

### Table 2 A comparison of knowledge, attitude, and practice scores for breast cancer among 1346 female college students (n = 1346, mean ± SD)

<table>
<thead>
<tr>
<th>Project</th>
<th>Knowledge score</th>
<th>t/F</th>
<th>P value</th>
<th>Attitude score</th>
<th>t/F</th>
<th>P value</th>
<th>Practice score</th>
<th>t/F</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 20</td>
<td>9.72 ± 2.42</td>
<td>11.548</td>
<td>0.000</td>
<td>3.07 ± 1.93</td>
<td>10.460</td>
<td>0.014</td>
<td>13.14 ± 2.44</td>
<td>16.987</td>
<td>0.000</td>
</tr>
<tr>
<td>21-25</td>
<td>10.53 ± 2.72</td>
<td></td>
<td></td>
<td>3.82 ± 2.21</td>
<td></td>
<td></td>
<td>14.17 ± 2.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 25</td>
<td>12.67 ± 5.13</td>
<td></td>
<td></td>
<td>6.00 ± 4.00</td>
<td></td>
<td></td>
<td>15.33 ± 3.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han</td>
<td>9.89 ± 2.45</td>
<td>1.131</td>
<td>0.335</td>
<td>3.18 ± 2.02</td>
<td>0.485</td>
<td>0.901</td>
<td>13.31 ± 2.51</td>
<td>0.916</td>
<td>0.522</td>
</tr>
<tr>
<td>Yi</td>
<td>9.42 ± 2.61</td>
<td></td>
<td></td>
<td>3.19 ± 2.00</td>
<td></td>
<td></td>
<td>13.48 ± 2.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bai</td>
<td>10.20 ± 2.74</td>
<td></td>
<td></td>
<td>3.39 ± 1.73</td>
<td></td>
<td></td>
<td>13.27 ± 1.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hui</td>
<td>10.11 ± 2.76</td>
<td></td>
<td></td>
<td>3.00 ± 2.50</td>
<td></td>
<td></td>
<td>13.22 ± 3.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhuang</td>
<td>9.74 ± 3.29</td>
<td></td>
<td></td>
<td>2.80 ± 1.49</td>
<td></td>
<td></td>
<td>12.42 ± 2.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ha Ni</td>
<td>9.63 ± 2.11</td>
<td></td>
<td></td>
<td>3.74 ± 1.99</td>
<td></td>
<td></td>
<td>13.26 ± 2.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dai</td>
<td>10.82 ± 2.46</td>
<td></td>
<td></td>
<td>3.31 ± 2.06</td>
<td></td>
<td></td>
<td>13.59 ± 2.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miao</td>
<td>8.93 ± 2.25</td>
<td></td>
<td></td>
<td>3.47 ± 2.00</td>
<td></td>
<td></td>
<td>13.07 ± 1.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li Su</td>
<td>9.83 ± 2.33</td>
<td></td>
<td></td>
<td>2.83 ± 1.19</td>
<td></td>
<td></td>
<td>13.58 ± 2.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na Xi</td>
<td>10.36 ± 2.66</td>
<td></td>
<td></td>
<td>3.27 ± 1.62</td>
<td></td>
<td></td>
<td>14.63 ± 2.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>9.67 ± 2.47</td>
<td></td>
<td></td>
<td>3.31 ± 2.19</td>
<td></td>
<td></td>
<td>13.10 ± 2.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>9.32 ± 2.30</td>
<td>45.996</td>
<td>0.000</td>
<td>2.80 ± 1.73</td>
<td>36.480</td>
<td>0.000</td>
<td>12.87 ± 2.29</td>
<td>39.017</td>
<td>0.000</td>
</tr>
<tr>
<td>Second</td>
<td>10.35 ± 2.39</td>
<td></td>
<td></td>
<td>3.51 ± 2.22</td>
<td></td>
<td></td>
<td>13.25 ± 2.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>10.69 ± 2.64</td>
<td></td>
<td></td>
<td>3.84 ± 2.22</td>
<td></td>
<td></td>
<td>14.21 ± 2.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registered residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>9.84 ± 2.56</td>
<td>0.169</td>
<td>0.866</td>
<td>3.60 ± 2.23</td>
<td>3.647</td>
<td>0.000</td>
<td>13.79 ± 2.52</td>
<td>3.850</td>
<td>0.000</td>
</tr>
<tr>
<td>Rural</td>
<td>9.86 ± 2.48</td>
<td></td>
<td></td>
<td>3.08 ± 1.93</td>
<td></td>
<td></td>
<td>13.17 ± 2.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>9.88 ± 2.51</td>
<td>1.657</td>
<td>0.191</td>
<td>3.20 ± 1.98</td>
<td>3.781</td>
<td>0.024</td>
<td>13.44 ± 2.37</td>
<td>6.505</td>
<td>0.002</td>
</tr>
<tr>
<td>Nonmedical science</td>
<td>9.53 ± 2.27</td>
<td></td>
<td></td>
<td>2.85 ± 1.79</td>
<td></td>
<td></td>
<td>12.60 ± 2.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonmedical arts</td>
<td>9.98 ± 2.59</td>
<td></td>
<td></td>
<td>3.39 ± 2.20</td>
<td></td>
<td></td>
<td>13.25 ± 2.68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3 Multiple linear regression analysis of the factors that influence knowledge, attitude, and practice scores for breast cancer, age was included directly in this analysis as a form of measurement data

<table>
<thead>
<tr>
<th>Project</th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant term</td>
<td>7.335</td>
<td>1.228</td>
<td>-</td>
<td>5.976</td>
<td>0.000</td>
</tr>
<tr>
<td>Grade</td>
<td>0.635</td>
<td>0.098</td>
<td>0.226</td>
<td>6.494</td>
<td>0.000</td>
</tr>
<tr>
<td>Attitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant term</td>
<td>1.627</td>
<td>0.985</td>
<td>-</td>
<td>1.652</td>
<td>0.099</td>
</tr>
<tr>
<td>Registered residence</td>
<td>-0.542</td>
<td>0.129</td>
<td>-0.112</td>
<td>-4.212</td>
<td>0.000</td>
</tr>
<tr>
<td>Grade</td>
<td>0.448</td>
<td>0.079</td>
<td>0.198</td>
<td>5.713</td>
<td>0.000</td>
</tr>
<tr>
<td>Practice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant term</td>
<td>11.005</td>
<td>1.218</td>
<td>-</td>
<td>9.038</td>
<td>0.000</td>
</tr>
<tr>
<td>Age</td>
<td>0.156</td>
<td>0.068</td>
<td>0.080</td>
<td>2.288</td>
<td>0.022</td>
</tr>
<tr>
<td>Registered residence</td>
<td>-0.691</td>
<td>0.159</td>
<td>-0.115</td>
<td>-4.343</td>
<td>0.000</td>
</tr>
<tr>
<td>Grade</td>
<td>0.522</td>
<td>0.097</td>
<td>0.186</td>
<td>5.376</td>
<td>0.000</td>
</tr>
<tr>
<td>Major</td>
<td>-0.217</td>
<td>0.084</td>
<td>-0.068</td>
<td>-2.569</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Table 4 Multiple linear regression analysis of the factors that influence knowledge, attitude, and practice scores for breast cancer, age was included directly in the analysis as ranked data

<table>
<thead>
<tr>
<th>Project</th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant term</td>
<td>8.646</td>
<td>0.379</td>
<td>-</td>
<td>22.791</td>
<td>0.000</td>
</tr>
<tr>
<td>Grade</td>
<td>0.704</td>
<td>0.087</td>
<td>0.250</td>
<td>8.096</td>
<td>0.000</td>
</tr>
<tr>
<td>Attitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant term</td>
<td>2.977</td>
<td>0.304</td>
<td>-</td>
<td>9.788</td>
<td>0.000</td>
</tr>
<tr>
<td>Registered residence</td>
<td>-0.537</td>
<td>0.128</td>
<td>-0.111</td>
<td>-4.180</td>
<td>0.000</td>
</tr>
<tr>
<td>Grade</td>
<td>0.473</td>
<td>0.070</td>
<td>0.209</td>
<td>6.777</td>
<td>0.000</td>
</tr>
<tr>
<td>Practice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant term</td>
<td>13.407</td>
<td>0.376</td>
<td>-</td>
<td>35.622</td>
<td>0.000</td>
</tr>
<tr>
<td>Registered residence</td>
<td>-0.677</td>
<td>0.159</td>
<td>-0.113</td>
<td>-4.260</td>
<td>0.000</td>
</tr>
<tr>
<td>Grade</td>
<td>0.583</td>
<td>0.086</td>
<td>0.208</td>
<td>6.752</td>
<td>0.000</td>
</tr>
<tr>
<td>Major</td>
<td>-0.193</td>
<td>0.084</td>
<td>-0.061</td>
<td>-2.292</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Information related to the KAP questionnaire for breast cancer

Analysis showed that 29.7% of respondents were unwilling to communicate with their friends or family with regards to breast-related problems; 30.1% of respondents did not consider that the early onset of menstruation, or a later menopause, were associated with breast cancer; 19.8% did not consider that fertility or infertility was associated with breast cancer after 30 years of age, and 14.6% of respondents did not believe that breastfeeding could reduce the incidence of breast cancer. Analysis also showed that 54.5% of our respondents did not know about breast self-examination and that 76.3% of respondents did not examine their own breasts; 74.2% did not know the best time for self-examination; 72.8% respondents did not know the common technical examination for breast cancer; and 74.5% of respondents did not know how often adult women should undergo clinical examinations of their breasts. Furthermore, 56.3% of respondents did not know that mammography could detect early breast cancer that could not be detected by palpation and 50.0% of respondents had no access to healthcare knowledge related to breast cancer (Table 5).

DISCUSSION

The number of younger patients (≤ 35 year of age) accounts for 7% of patients with breast cancer. These younger patients with breast cancer are associated with high levels of malignancy, rapid progression, early metastasis, and a poor prognosis[12]. Screening and prevention strategies are known to exert a significant effect on reducing
Table 5 Statistics related to the knowledge, attitude, and practice questionnaire for the breast cancer

<table>
<thead>
<tr>
<th>Subject</th>
<th>Number of people (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have a history of breast disease</td>
<td>Yes: 15 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 200 (14.4)</td>
</tr>
<tr>
<td></td>
<td>No: 1172 (84.5)</td>
</tr>
<tr>
<td>Have had a breast mass</td>
<td>Yes: 57 (4.1)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 334 (24.1)</td>
</tr>
<tr>
<td></td>
<td>No: 996 (71.8)</td>
</tr>
<tr>
<td>Share breast-related issues with friends or family</td>
<td>Yes: 682 (49.2)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 293 (21.1)</td>
</tr>
<tr>
<td></td>
<td>No: 412 (29.7)</td>
</tr>
<tr>
<td>Have a family history of breast cancer (Female relatives in the family have or have had breast cancer)</td>
<td>Yes: 53 (3.8)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 204 (14.7)</td>
</tr>
<tr>
<td></td>
<td>No: 1130 (81.5)</td>
</tr>
<tr>
<td>Early menarche and late menopause associated with breast cancer</td>
<td>Yes: 301 (21.7)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 669 (48.2)</td>
</tr>
<tr>
<td></td>
<td>No: 417 (30.1)</td>
</tr>
<tr>
<td>Fertility or infertility after 30 years old related to breast cancer</td>
<td>Yes: 279 (20.1)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 833 (60.1)</td>
</tr>
<tr>
<td></td>
<td>No: 275 (19.8)</td>
</tr>
<tr>
<td>Breastfeeding reduce the incidence rate of breast cancer</td>
<td>Yes: 369 (26.6)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 816 (58.8)</td>
</tr>
<tr>
<td></td>
<td>No: 202 (14.6)</td>
</tr>
<tr>
<td>No mass in the breast but in the armpit be highly vigilant</td>
<td>Yes: 1053 (75.9)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 305 (22.0)</td>
</tr>
<tr>
<td></td>
<td>No: 29 (2.1)</td>
</tr>
<tr>
<td>Bloody secretions from the breast a bad sign of breast cancer</td>
<td>Yes: 684 (49.3)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 660 (47.6)</td>
</tr>
<tr>
<td></td>
<td>No: 43 (3.1)</td>
</tr>
<tr>
<td>If breast pain and/or breast skin changes is breast cancer performance</td>
<td>Yes: 481 (34.7)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 819 (59.0)</td>
</tr>
<tr>
<td></td>
<td>No: 87 (6.3)</td>
</tr>
<tr>
<td>If nipple invagination should remain vigilant</td>
<td>Yes: 992 (71.5)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 326 (23.5)</td>
</tr>
<tr>
<td></td>
<td>No: 69 (5.0)</td>
</tr>
<tr>
<td>Know about breast self-examination</td>
<td>Yes: 183 (13.2)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 448 (32.3)</td>
</tr>
<tr>
<td></td>
<td>No: 756 (54.5)</td>
</tr>
<tr>
<td>Have done breast self-examination</td>
<td>Yes: 70 (5.0)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 288 (20.8)</td>
</tr>
<tr>
<td></td>
<td>No: 1029 (74.2)</td>
</tr>
<tr>
<td>Know the common technical examination methods of breast</td>
<td>Yes: 118 (8.5)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 259 (18.7)</td>
</tr>
<tr>
<td></td>
<td>No: 1010 (72.8)</td>
</tr>
<tr>
<td>Know how often adult women do breast clinical examination at least</td>
<td>Yes: 70 (5.0)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 284 (20.5)</td>
</tr>
<tr>
<td></td>
<td>No: 1033 (74.5)</td>
</tr>
<tr>
<td>Accept genetic screening if genetic testing can predict breast cancer</td>
<td>Yes: 1085 (78.2)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 208 (15.0)</td>
</tr>
<tr>
<td></td>
<td>No: 94 (6.8)</td>
</tr>
<tr>
<td>Know mammography can detect early breast cancer but cannot be detected by palpation</td>
<td>Yes: 187 (13.5)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 419 (30.2)</td>
</tr>
<tr>
<td></td>
<td>No: 781 (56.3)</td>
</tr>
<tr>
<td>Willing to accept breast disease prevention guidance and take the initiative to carry out breast self-examination</td>
<td>Yes: 1172 (84.5)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 151 (10.9)</td>
</tr>
<tr>
<td></td>
<td>No: 64 (4.6)</td>
</tr>
<tr>
<td>Find breast abnormality or discomfort, take the initiative to seek medical treatment in time</td>
<td>Yes: 1025 (73.9)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 253 (18.2)</td>
</tr>
<tr>
<td></td>
<td>No: 109 (7.9)</td>
</tr>
<tr>
<td>A way to acquire breast health knowledge</td>
<td>Yes: 413 (29.8)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 281 (20.3)</td>
</tr>
<tr>
<td></td>
<td>No: 693 (50.0)</td>
</tr>
<tr>
<td>Women should receive health education on breast cancer</td>
<td>Yes: 1279 (92.2)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 85 (6.1)</td>
</tr>
<tr>
<td></td>
<td>No: 19 (1.4)</td>
</tr>
<tr>
<td></td>
<td>Oppose: 4 (0.3)</td>
</tr>
<tr>
<td>Take the initiative to prevent breast cancer in daily life</td>
<td>Yes: 1308 (94.3)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 46 (3.3)</td>
</tr>
<tr>
<td></td>
<td>No: 31 (2.2)</td>
</tr>
<tr>
<td></td>
<td>Oppose: 2 (0.1)</td>
</tr>
<tr>
<td>Accept breast resection to save life</td>
<td>Yes: 820 (59.1)</td>
</tr>
<tr>
<td></td>
<td>Uncertain: 227 (16.4)</td>
</tr>
<tr>
<td></td>
<td>No: 288 (20.8)</td>
</tr>
<tr>
<td></td>
<td>Oppose: 52 (3.7)</td>
</tr>
</tbody>
</table>

the incidence rate of breast cancer[3-5]. Research studies have also focus on the prevention of breast cancer in younger women[13].

In the present study, we demonstrated that the main factor that influences breast cancer knowledge in female college students in western Yunnan was their grades. We identified a correlation between age and grade, as reported previously by Zhou et al [3]. Irrespective of whether age was included in our calculations as ranked data or measurement data, the influence of grade, as an independent variable, on the knowledge score was statistically significant. Therefore, the imbalance in breast cancer knowledge and education among female college students between different ages and grades is a critical factor that needs to be addressed. Other population characteristics should also be considered; female college students with a low age, low grade, and a low educational background, can be regarded as a key population for health education. In addition, we found that 14.4%–24.1% of respondents were not sure about their breast history and their family history of breast cancer. Familial cases of breast cancer can result in changes in the KAP values of women from affected families when compared to unaffacted families; this was not considered in the present study.

Furthermore, 30.1% of respondents did not believe that the early onset of menstruation and a later menopause was associated with breast cancer. Analysis also showed that 19.8% of respondents did not consider that fertility or infertility was associated with breast cancer after 30 years of age, and 14.6% did not believe that breastfeeding could reduce the incidence rate of breast cancer. The total awareness rate of breast cancer among female college students was 54.66%; this was higher than the
rates that have been published previously (32.8%-51.38%)\cite{14}, but still demonstrated imbalance (20.1%-85.6%). In particular, the insufficient awareness of high-risk factors for breast cancer should represent a key aspect of primary prevention and needs to be addressed.

In this research study, we found that the main factors that influenced attitude scores were registered residence and grade. The attitude scores for senior and urban female college students were higher than those who were junior and rural; these findings were consistent with previous findings\cite{9,15}. Female college students in western Yunnan are more considerate with regards to seeking health care for the precancerous signs of breast cancer, although 56.3%-74.5% of respondents lacked a positive attitude for common technical examination methods, examination times, and mammography examinations. With regards to the early screening of breast cancer, mammography is considered to be the only screening method that can reduce the mortality rate associated with breast cancer\cite{16} as this method can accurately detect small lumps along with typical granular and tiny burry calcifications. However, mammography is highly sensitive to the location of pathological tissue and breast morphology, and is not unsuitable for Chinese women with dense glands and small breasts\cite{17}. In a previous study, Guo et al\cite{18} reported that breast ultrasound is an easy technique to carry out and is both safe and non-invasive; however, mammography is widely used due to its high levels of sensitivity and specificity. Both of these techniques have their own advantages and limitations. Therefore, we advocate that the combined application of mammography and ultrasound should be used to screen for early breast cancer. With regards to the female college students in western Yunnan, and especially for those with lower grades and who reside in rural areas, it is particularly important that we increase publicity relating to early breast cancer screening and introduce more rigorous preventive education strategies. For young women with a family history and the presence of a breast mass, we advocate the use of a combination of mammography and ultrasound as a routine physical examination.

In this research, we found that the main influencing factors for behavior included age, registered residence, grade and major. Therefore, the behavior of female college students in western Yunnan is both comprehensive and multifactorial. However, low age, a rural residence, a low grade, a non-medical major, and a reluctance to talk about breast cancer and self-examination are identified as key factors, particularly self-examination. Overall, 13.2% of our respondents knew more about breast self-examination; this was greater than the proportion reported by Jiang et al\cite{9} (12%) but less than that reported by Wang et al\cite{15} (41.10%). Analysis further showed that 14.8% of our respondents had examined their breasts; this was less than the proportion reported by Jiang et al\cite{9}. Moreover, 5.0% of respondents knew the best time for breast self-examination; this was less than the proportion reported previously by Lei et al\cite{19} (6.7%). We also found that 29.7% of respondents were unwilling to communicate with friends or family about breast-related problems.

It is evident, therefore, that female college students in western Yunnan were seriously lacking in the knowledge and skills required for breast examination. It is suggested that publicity should be strengthened through audio-visual media, classroom education, practical training, and other methods. These students should also be encouraged to overcome their shyness and carry out early self-examination.

Over recent years, breast cancer has become a very common form of tumor. Differences in culture, lifestyle, and social demography, are known to affect the biological expression of breast cancer, thus leading to different incidences and mortality rates. The responses to our questionnaire demonstrated that female college students in western Yunnan have low awareness of breast cancer, cognitive deficiencies and imbalances, and a low rate of breast self-examination. To improve the physical qualities of our female population of students, it is vital that we improve breast cancer knowledge on university campuses and develop more ways to improve the understanding of breast cancer among young female college students; this will reduce incidence rates in the younger population. It is also important that we use plain language and concise words to carry out health education strategies for female college students relating to breast cancer, symptoms, therapeutic methods, and how to prevent this condition.

Familial cases of breast cancer can result in changes in the KAP values of women from affected families when compared to unaffected families; this was not considered in the present study.
CONCLUSION

In conclusion, there is an urgently need to provide standardized publicity and educational strategies in order to improve the knowledge levels of breast cancer of college students so as to reduce the incidence of breast cancer.

ARTICLE HIGHLIGHTS

Research background
Morbidity of breast cancer become younger, many female college students have insufficient awareness of breast health care and breast cancer.

Research motivation
It’s not reported that knowledge of breast cancer and health care of female college students in western Yunnan.

Research objectives
We want to know about knowledge of breast cancer in female college students and take some measures.

Research methods
We designed the questionnaire and totally 1387 questionnaires were sent out.

Research results
Influence factor of breast cancer knowledge is grade, influence factors of breast cancer attitude are registered residence and grade, influence factors of breast cancer practice are registered residence, grade and major.

Research conclusions
The knowledge, attitude, and practice level of female college students in western Yunnan were low, health education and self-examination of breast cancer is necessary.

Research perspectives
Using specific questionnaires, we identified a low awareness for breast cancer in female college students in west Yunnan, along with cognitive loopholes and imbalance in different ages and different grades.

REFERENCES

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Observational Study

Diagnosing early scar pregnancy in the lower uterine segment after cesarean section by intracavitary ultrasound

Xiao-Ling Cheng, Xiao-Yan Cao, Xiao-Qian Wang, Heng-Li Lin, Jin-Chuan Fang, Lin Wang

ORCID number: Xiao-Ling Cheng 0000-0002-4654-7728; Xiao-Yan Cao 0000-0002-7443-3357; Xiao-Qian Wang 0000-0001-9173-7910; Heng-Li Lin 0000-0002-7230-5052; Jin-Chuan Fang 0000-0002-7533-4465; Lin Wang 0000-0001-8850-9386.

Author contributions: Cheng XL and Cao XY design the experiment; Wang XQ drafted the work, Lin HL and Fang JC collected the data; Wang L and Cheng XL analysed and interpreted data, Cao XY and Wang XQ wrote the manuscript; all authors read and proofed the revised manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Women and Children Health Institute Futian Shenzhen.

Informed consent statement: Informed consents were obtained from all patients and their families.

Conflict-of-interest statement: The authors declared that there is no conflict of interest among them.

Data sharing statement: No additional data are available.

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

Abstract

BACKGROUND

Early scar pregnancy (CSP) in the lower uterine segment after cesarean section is a type of ectopic pregnancy that can cause major complications if left untreated. Transabdominal ultrasound is a common procedure but is influenced by external factors. Thus, intracavitary ultrasound may have better diagnostic efficiency for CSP.

AIM

To assess the value of intracavitary ultrasound for diagnosing CSP in the lower uterine segment after cesarean section.

METHODS

Patients diagnosed with CSP in our hospital from October 2019 to April 2021 were recruited. Transabdominal and intracavitary ultrasound examinations were performed to compare the diagnostic differences for CSP and its types.

RESULTS

Sixty-three patients were diagnosed during the study period. The diagnostic accuracy for CSP was higher in intracavitary ultrasound (96.83%) than in transabdominal ultrasound (84.13%) \((P < 0.05)\). The missed diagnosis and misdiagnosis rates did not differ among the ultrasound types (intra: 0.00% and 3.17%; trans: 4.76% and 11.11%, respectively; \(P > 0.05\)). For the diagnostic rates for the CSP types, the rates for gestational sac (100.00% vs 90.48%), heterogeneous mass (93.75% vs 75.00%), and part of the uterine cavity (80.00% vs 60.00%) were higher in intracavitary ultrasound than in transabdominal ultrasound, but the difference was not statistically significant \((P > 0.05)\). For gestational sac CSP patients, intracavitary ultrasound showed that the gestational sac was located in the lower uterine segment scar with abundant peripheral blood flow; the distance between the gestational sac and the serosal layer was 2.42 ± 0.50 cm. Intracavitary ultra-
MATERIALS AND METHODS

Patient selection
This study was approved by the ethics committee of our hospital, and informed consent was obtained from all patients and their families. Patients diagnosed with CSP in our hospital from October 2019 to April 2021 were recruited. The inclusion criteria for heterogeneous mass CSP patients indicated that the mass mainly occurred in the lower anterior uterine wall, protruding into the bladder, and was surrounded by abundant internal and peripheral blood flow; the distance between the mass and serosal layer was 1.79 \pm 0.30 \text{cm}. For CSP type partly located in the uterine cavity, the gestational sac was partly located in the lower uterine cavity and partly in the scar with abundant internal and peripheral blood flow; the distance between the gestational sac and the serosal layer was 2.29 \pm 0.28 \text{cm}.

CONCLUSION
Intracavitary ultrasound had a higher diagnostic accuracy and application value for diagnosing CSP than transabdominal ultrasound, with reduced risk of missed diagnoses and misdiagnosis, thereby preventing delayed treatment.

Key Words: Ultrasonography; Cesarean section; Uterus; Pregnancy; Cesarean section; Repeat; Ultrasonography; Doppler

Core Tip: This study assessed the value of using intracavitary ultrasound for diagnosing early scar pregnancy after cesarean section and found that it had higher diagnostic accuracy than traditional transabdominal ultrasound, reducing the risk of missed diagnosis and misdiagnosis, likely resulting in prompt treatment and improved patient prognosis.

INTRODUCTION
Early scar pregnancy (CSP) in the lower uterine segment after cesarean section is primarily an embryonic pregnancy at the lower uterine segment incision scar, also known as an incision pregnancy, which is a type of ectopic pregnancy\(^1,2\). In recent years, the CSP incidence has risen, threatening patients’ physical and mental health and quality of life with increasing cesarean section rates\(^3,4\). If an embryo implants into the site of the lower uterine scar from a previous cesarean, and timely and accurate diagnosis and treatment is not provided, then the implantation and adhesion of villi and myometrium can cause uncontrollable massive bleeding, and, in severe cases, uterine rupture as the pregnancy progresses\(^5,6\). Consequently, early CSP diagnosis remains a critical research topic.

Ultrasound is a commonly used diagnostic modality. Traditional abdominal ultrasound is easily affected by external factors, such as abdominal fat thickness and poor bladder filling, leading to an increased risk of misdiagnosis. However, an intracavitary ultrasound resists the influences of external factors on the diagnostic results\(^7,8\).

This study compared the diagnostic value of intracavitary and transabdominal ultrasound for diagnosing CSP and its types.
were as follows: (1) A history of cesarean section; (2) The interval between current and previous cesarean sections was more than one year; (3) The previous cesarean section incision was transverse and healed well; (4) The patient was mentally fit and could cooperate with the researchers to complete the investigation; (5) An abnormally increased human chorionic gonadotropin level; and (6) Variable degrees of abdominal pain and irregular vaginal bleeding.

The exclusion criteria were as follows, patients with: (1) Organic diseases, such as kidney, liver, and heart disease; (2) Malignant tumors; (3) Speech communication disorders, hearing impairment, or mental system disease; and (4) Poor compliance and who were unable to cooperate to complete the survey.

**Transabdominal ultrasonography**
All patients were examined by transabdominal and intracavitary ultrasonography. The Toshiba LOGIQ S7 type four-dimensional color Doppler ultrasound diagnostic instrument and matching ultrasound probe were used for the transabdominal ultrasound. When the patient’s bladder was full, an assistant helped the patient into a supine position. An ultrasound probe with 5-9 MHz was smeared on the coupling agent and placed on the lower abdomen for examination to determine the position, size, and appendages of the uterine pregnancy and investigate the myometrium thickness, abnormal mass around the uterus, myometrial defects, and incision scar.

**Intracavitary ultrasonography**
The equipment and probe frequency of intracavitary ultrasonography were the same as those of transabdominal ultrasonography. The probe smeared on the coupling agent was placed on the condom. Iodophor (2%) was evenly applied on the outside of the condom, then slowly inserted into the vagina to perform longitudinal and transverse scanning at the uterine incision, pregnancy site, cervix, uterine cavity, bilateral accessories, and pelvic cavity, and investigate the myometrium thickness, the gestational sac implantation position, scar blood flow, and incision echo.

**Observation index**
CSP diagnosis by transabdominal and intracavitary ultrasonography were analyzed, as were the CSP types, including gestational sac, heterogeneous mass, and part of the uterine cavity.

**Statistical analyses**
Data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Measurement data were expressed as means ± SD, and the data were expressed as n (%). A P value of < 0.05 indicated statistical significance.

**RESULTS**

**Patient demographics**
In total, 63 patients with CSP were included, with an average age of 29.56 ± 64 (range, 23 to 36) years. The average gravidity was 2.48 ± 1.10 (range, 1 to 4) times. The average interval between the current and previous cesarean sections was 4.63 ± 2.91 (range, 1 to 8) years. The average menopause duration was 51.41 ± 13.91 (range, 36 to 67) d.

**Examination methods and CSP diagnoses**
The diagnostic accuracy was significantly higher in intracavitary ultrasonography (96.83%) than in transabdominal ultrasonography (84.13%; P < 0.05). The missed diagnosis and misdiagnosis rates did not differ between the two methods (intra: 0.00% and 3.17%; trans: 4.76% and 11.11%, respectively; P > 0.05; Table 1).

**Examination methods and diagnosing CSP types**
The intracavitary ultrasound diagnostic rates were higher than the transabdominal ultrasound diagnostic rates, but the difference was not statistically significant for the gestational sac (100.00% vs 90.48%), heterogeneous mass (93.75% vs 75.00%), and part-of-the-uterine-cavity (80.00% vs 60.00%) types (P > 0.05; Table 2).
**Table 1 Early scar pregnancy diagnoses by examination method, n (%)**

<table>
<thead>
<tr>
<th>Method</th>
<th>Cases</th>
<th>Accuracy</th>
<th>Missed diagnosis</th>
<th>Misdiagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracavitary</td>
<td>63</td>
<td>61 (96.83)</td>
<td>0 (0.00)</td>
<td>2 (3.17)</td>
</tr>
<tr>
<td>Transabdominal</td>
<td>63</td>
<td>53 (84.13)</td>
<td>3 (4.76)</td>
<td>7 (11.11)</td>
</tr>
</tbody>
</table>

χ² value 4.513  P value 0.034

**Table 2 Examination methods and the diagnostic accuracy for early scar pregnancy types, n (%)**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Cases</th>
<th>Gestational sac</th>
<th>Heterogeneous mass</th>
<th>Uterine cavity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracavitary</td>
<td>63</td>
<td>42/42 (100.00)</td>
<td>15/16 (93.75)</td>
<td>4/5 (80.00)</td>
<td>61/63 (96.83)</td>
</tr>
<tr>
<td>Transabdominal</td>
<td>63</td>
<td>38/42 (90.48)</td>
<td>12/16 (75.00)</td>
<td>3/5 (60.00)</td>
<td>53/63 (84.13)</td>
</tr>
</tbody>
</table>

χ² value 2.363  P value 0.124

**Intracavitary ultrasonography and CSP types**

Intracavitary ultrasonography for the gestational sac CSP type showed that the gestational sac was located on the scar of the lower uterine segment with abundant peripheral blood flow, and the distance between the gestational sac and the serosal layer was 2.42 ± 0.50 cm. For the heterogeneous mass type, the heterogeneous mass was located on the lower anterior uterine wall, protruding into the bladder, and was surrounded by abundant internal and peripheral blood flow; the distance between the mass and serosal layer was 1.79 ± 0.30 cm. For the part-of-the-uterine-cavity CSP type, the gestational sac was located partly in the lower uterine cavity and partly in the scar and surrounded by abundant internal and peripheral blood flow; the distance between the gestational sac and the serosal layer was 2.29 ± 0.28 cm (Table 3).

**DISCUSSION**

CSP, a multiple ectopic pregnancy type, has a complex pathogenic mechanism that has yet to be clarified[9-11]. However, some studies have suggested that CSP is closely related to abnormal changes in local biochemical factors and the anatomical status of the uterine incision scar[12]. Others suggested that CSP is associated with decidual vascular defects, poor wound healing, and endometrial injury[13,14]. Further, typical clinical CSP manifestations are lacking. Thus, there is a high risk of missed diagnosis or misdiagnosis. Correctly diagnosing CSP soon after a cesarean section is difficult, and the optimal time to diagnose CSP is unclear. Consequently, the initial treatment plan may be ineffective, increasing the risk of uncontrollable massive hemorrhage, uterine rupture, and other adverse events. Severe cases require a hysterectomy, seriously affecting the psychological and physical health of these patients.

In recent years, the social economy and medical technology have continuously developed. For CSP, color Doppler ultrasound can determine the scar blood flow, muscle layer thickness, and gestational sac implantation, which is advantageous for diagnosing and evaluating the treatment[15]. However, the traditional transabdominal ultrasound is limited by abdominal fat and intestinal gas and requires a full bladder, resulting in a low accuracy. Conversely, in intracavitary ultrasound, these adverse diagnostic effects are avoided and the probe is as close to the abdominal cavity as possible, which is beneficial for obtaining the information needed for a diagnosis, improving the diagnostic accuracy[16].

CSP grows in two ways. In one, growth starts from the scar and orients toward the uterine cavity, making continuous growth and survival possible. In the second, growth starts from the scar but orients toward the uterine wall, resulting in an intramuscular pregnancy and possibly uterine rupture, perforation, or abortion. With the continuous development of eggs, the gestational sac and viable germ may occur in the uterine cavity based on the intrauterine ultrasound examination and some pregnant tissues and placenta accreta at the incision[17,18]. The lack of specific clinical CSP manifest-
Table 3 Intracavitary ultrasound for diagnosing early scar pregnancy types

<table>
<thead>
<tr>
<th>Types</th>
<th>Cases</th>
<th>Performance</th>
<th>Blood flow</th>
<th>Interval (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational sac</td>
<td>42</td>
<td>The gestational sac was located in the scar of the lower uterine segment</td>
<td>Abundant peripheral blood flow</td>
<td>2.42 ± 0.50</td>
</tr>
<tr>
<td>Heterogeneous mass</td>
<td>16</td>
<td>The heterogeneous mass was located in the lower part of the anterior wall of uterus, protruding into the bladder</td>
<td>Abundant internal and peripheral blood flow</td>
<td>1.79 ± 0.30</td>
</tr>
<tr>
<td>Part of the uterine cavity</td>
<td>5</td>
<td>The gestational sac was located in the lower part of the uterine cavity and part in the scar</td>
<td>Abundant internal and peripheral blood flow</td>
<td>2.29 ± 0.28</td>
</tr>
</tbody>
</table>

Intracavitary ultrasound has a higher diagnostic accuracy and, therefore, higher application value for diagnosing CSP than traditional transabdominal ultrasound. Intracavitary ultrasound reduces the risk of missed diagnosis and misdiagnosis, likely resulting in prompt treatment and improved patient prognosis. However, the sample size of this study is small; thus, to determine whether our conclusions are broadly valid, the scope of selected cases and the number of study cases should be expanded for in-depth exploration.

CONCLUSION

Intracavitary ultrasound has a higher diagnostic accuracy and, therefore, higher application value for diagnosing CSP than traditional transabdominal ultrasound. Intracavitary ultrasound reduces the risk of missed diagnosis and misdiagnosis, likely resulting in prompt treatment and improved patient prognosis. However, the sample size of this study is small; thus, to determine whether our conclusions are broadly valid, the scope of selected cases and the number of study cases should be expanded for in-depth exploration.

ARTICLE HIGHLIGHTS

Research background

Early scarring pregnancy (CSP) in the lower part of the uterus after cesarean section is an ectopic pregnancy. Intracavitary ultrasound may have a better diagnostic efficiency for CSP.
**Research motivation**
This study evaluated the value of intracavitary ultrasound in the diagnosis of CSP in the lower uterus after cesarean section.

**Research objectives**
In this manuscript, the authors aimed to study the value of intracavitary ultrasound in the diagnosis of CSP in the lower segment of the uterus after cesarean section, and to provide a better basis and method for the diagnosis of CSP.

**Research methods**
An observational study was conducted on patients diagnosed with CSP in our hospital from October 2019 to April 2021.

**Research results**
The diagnostic accuracy of intracavitary ultrasound for CSP is higher than that of transabdominal ultrasound. There was no difference between the missed diagnosis rate and the misdiagnosis rate between ultrasound types. For the diagnosis rate of CSP type, the diagnosis rate of pregnancy sac, heterogeneous mass and partial of the uterine cavity by intracavitary ultrasound is higher than that of transabdominal ultrasound, and the difference is not statistically significant.

**Research conclusions**
Intracavitary ultrasound had a higher diagnostic accuracy and application value for diagnosing CSP than transabdominal ultrasound, with reduced risk of missed diagnoses and misdiagnosis, thereby preventing delayed treatment.

**Research perspectives**
Intracavitary ultrasound may have a better diagnostic efficiency for CSP and has a wider clinical application value.

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Impact of failure mode and effects analysis-based emergency management on the effectiveness of craniocerebral injury treatment

Xiao-Lan Shao, Ya-Zhou Wang, Xiong-Hui Chen, Wen-Juan Ding

ORCID number: Xiao-Lan Shao 0000-0003-3659-8473; Ya-Zhou Wang 0000-0001-9201-3463; Xiong-Hui Chen 0000-0002-4866-0951; Wen-Juan Ding 0000-0001-5897-4914.

Author contributions: Shao XL and Wang YZ designed the experiment; Chen XH drafted the work, Chen XH collected the data; Ding WJ and Shao XL analyzed and interpreted data, Wang YZ and Chen XH wrote the manuscript.

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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.

Data sharing statement: No additional data are available.

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

Abstract

BACKGROUND
Craniocerebral injuries encompass brain injuries, skull fractures, cranial soft tissue injuries, and similar injuries. Recently, the incidence of craniocerebral injuries has increased dramatically due to the increased numbers of traffic accidents and aerial work injuries, threatening the physical and mental health of patients.

AIM
To investigate the impact of failure modes and effects analysis (FMEA)-based emergency management on craniocerebral injury treatment effectiveness.

METHODS
Eighty-four patients with craniocerebral injuries, treated at our hospital from November 2019 to March 2021, were selected and assigned, using the random number table method, to study (n = 42) and control (n = 42) groups. Patients in the control group received conventional management while those in the study group received FMEA theory-based emergency management, based on the control group. Pre- and post-interventions, details regarding the emergency situation; levels of inflammatory stress indicators [Interleukin-6 (IL-6), C-reactive protein (CRP), and procalcitonin (PCT)]; incidence of complications; prognoses; and satisfaction regarding patient care were evaluated for both groups.

RESULTS
For the study group, the assessed parameters [pre-hospital emergency response time (9.13 ± 2.37 min), time to receive a consultation (2.39 ± 0.44 min), time needed to report imaging findings (1.15 ± 4.44 min), and test reporting time (32.19 ± 6.23 min)] were shorter than those for the control group (12.78 ± 4.06 min, 3.58 ± 0.71 min, 33.49 ± 5.51 min, 50.41 ± 11.45 min, respectively; P < 0.05). Pre-intervention serum levels of IL-6 (78.71 ± 27.59 pg/mL), CRP (19.80 ± 6.77 mg/L), and PCT (3.66 ± 1.82 ng/mL) in the study group patients were not significantly different
from those in the control group patients (81.31 ± 32.11 pg/mL, 21.29 ± 8.02 mg/L, and 3.95 ± 2.11 ng/mL respectively; P > 0.05); post-intervention serum indicator levels were lower in both groups than pre-intervention levels. Further, serum levels of IL-6 (17.35 ± 5.33 pg/mL), CRP (2.27 ± 0.56 mg/L), and PCT (0.22 ± 0.07 ng/mL) were lower in the study group than in the control group (30.15 ± 12.38 pg/mL, 3.13 ± 0.77 mg/L, 0.38 ± 0.12 ng/mL, respectively; P < 0.05). The complication rate observed in the study group (9.52%) was lower than that in the control group (26.19%, P < 0.05). The prognoses for the study group patients were better than those for the control patients (P < 0.05). Patient care satisfaction was higher in the study group (95.24%) than in the control group (78.57%, P < 0.05).

CONCLUSION
FMEA-based craniocerebral injury management effectively shortens the time spent on emergency care, reduces inflammatory stress and complication risk levels, and helps improve patient prognoses, while achieving high patient care satisfaction levels.

Key Words: Craniocerebral injury; Failure modes and effects analysis theory; Emergency management; Treatment effect

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INTRODUCTION
Craniocerebral injuries are clinical emergencies that mainly occur as a direct result of external violence to the head, and include brain injuries, skull fractures, soft tissue injuries, and others. In recent years, increases in the numbers of traffic accidents and aerial work injuries has resulted in an increased incidence of craniocerebral injuries, threatening the physical and mental health of patients and limiting their quality of life [1-3]. Moreover, craniocerebral injuries are complex, progress rapidly, and have high disability and mortality rates. Failure to provide timely and effective intervention may affect the effectiveness of subsequent interventions, and may even be life threatening [4-6]. Therefore, timely and effective emergency care affects the prognosis and recovery of patients with craniocerebral injuries.

Failure mode and effects analysis (FMEA) is a clinically important care management model that can prospectively quantify the risk and causes of healthcare process failures; it also facilitates the development and implementation of interventions to reduce the incidence of events that put the health of patients at risk, thereby helping to ensure patient safety [7,8]. In addition, FMEA includes potential failure evaluation and analysis, and may be used to assess the consequences of and the implementation of interventions to address the occurrence of such failures. The use of FMEA has played an important role in the development of many disease interventions [9].

This study aimed to assess 84 cases of craniocerebral injury involving patients treated in our hospital, and explored the value of implementing an FMEA-based emergency management strategy using a group-control format.
MATERIALS AND METHODS

Selection criteria
Inclusion criteria: The inclusion criteria included a clear history of the causative injury; age > 18 and < 70 years; patients and family members able to understand the study; and voluntary provision of signed informed consent.

Exclusion criteria: The exclusion criteria included transferring out/dying during the study period, > 12 h between injury and admission, breastfeeding or pregnancy, poor compliance, and inability to complete the study.

Methods
The control group received conventional care, which included patient admission and pre-screening by nursing staff. The nursing staff also assisted craniocerebral injury patients throughout their initial diagnoses and related auxiliary examinations, and systematically reassessed patient conditions. The study group received FMEA theory-based emergency management, based on the control group: to clarify the failure mode and nursing themes, English databases were used; to clarify the failure modes and nursing topics, literature search data from English databases (Proquest Science Journal Database, Springer Link Science and Technology Journal Database, Elsevier Database, PubMed Medical Journal Database, etc.) were used.

To combine clinical nursing experience, a systematic assessment of the physical and mental status of patients, and the potential risk factors were identified using possible failure mode crisis values (RPNs). RPNs are calculated as severity \times frequency of occurrence \times difficulty of failure detection, with each factor scored from 1 to 10; higher scores indicate a greater likelihood of occurrence. Failure modes with high RPN scores in a comprehensive assessment were considered most important. The final analysis of failure modes included cumbersome procedures and resuscitation plans, and negative emotions. In response to the assessment of the above failure modes, care improvement focused on optimizing emergency procedures and protocols, alleviating negative emotions, restoring patient bodily functions, and developing targeted intervention plans.

Reception protocols were optimized as follows: patients with craniocerebral injuries were sent to the emergency resuscitation room immediately after admission; physicians were informed to launch a green channel; principles of consultation, examination, and treatment priority were strictly followed during the resuscitation process; and the patient’s condition was comprehensively assessed. Nurse-based resuscitation measures were optimized such that the resuscitation room nurses and mobile nurses formed an emergency care team with the following individual duties. The treatment nurse drew blood, performed electrocardiography, established intravenous access, and monitored oxygen saturation levels throughout the intervention. The resuscitation room nurse provided patient assistance to maintain a reasonable position, closely observed the patient’s condition, and maintained an open airway. The mobile nurse prepared the instruments required for resuscitation and administered oxygen, sputum inhalation prevention protocols, and other related treatments. The team leader strictly recorded the resuscitation process and the elapsed time during resuscitation.

The patient’s stay in the observation room was also optimized. After the resuscitation was complete, the following were monitored: patient condition, degree of consciousness, presence of adverse event precursors related to craniocerebral injury, immediately informing the physician of problems and providing assistance with response measures. Finally, health education and psychological interventions were strengthened. After the patient’s condition was stabilized, the patient’s education level, personality characteristics, and acceptance level were considered when providing health education and psychological guidance. Each patient was confirmed to have a basic knowledge of the disease, rehabilitation process, and precautions that should be taken. Further, each patient was encouraged to undergo treatment and rehabilitation with a positive and optimistic outlook.

Indicators
Five indicators were reviewed. (1) The emergency care of patients in both groups was assessed, including the duration of pre-hospital emergency response measures, and time spent receiving the patient, reporting imaging findings, and reporting clinical test findings; (2) Levels of inflammatory stress indicators [Interleukin-6 (IL-6), C-reactive protein (CRP), and procalcitonin (PCT)] were measured in both groups pre- and post-
intervention. Blood samples were centrifuged (3500 rpm, 15 min) and an enzyme-linked immunosorbent assay was used to determine levels of stress indicators in sample supernatants; (3) The incidences of complications, in both groups, were determined; (4) The prognoses of the patients in both groups were assessed using the Glasgow prognostic score, as follows: grade 5, good (able to work and study); grade 4, moderate disability (able to live on their own); grade 3, severe disability (requires care for daily work and life activities); grade 2, vegetative survival; and grade 1, death from disease; and (5) Statistics regarding satisfaction with nursing care were assessed in both groups using the Newcastle Satisfaction with Nursing Scale, which contains 19 items out of 95. Scores > 85 indicated that patients were very satisfied, 67–85 indicated that patients were generally satisfied, and scores < 67 indicated patient dissatisfaction. Satisfaction was calculated as follows: satisfaction = (generally satisfied + very satisfied)/total number of cases in the group × 100%.

Statistical analysis
Data were analyzed using SPSS 22.0 (IBM, Armonk, NY, USA). Measurements were compared using the t-test (means ± SD) or the χ2 test \[ n \text{ (%)} \]; ranked data were evaluated using the rank sum test; \( P \) values < 0.05 were considered statistically significant.

RESULTS
Eighty-four patients with craniocerebral injuries, treated at our hospital from November 2019 to March 2021, were selected and assigned, using the random number table method, into study (n = 42) and control (n = 42) groups. Twenty-three males and 19 females were included in the study group. The study-group patients were 22–68 years old (mean. 45.91 ± 13.19 years); had injuries caused by traffic accidents (21 cases), falls from heights (15 cases), heavy object trauma (5 cases), and other (1 case); and had primary school (13 patients), junior high school and high school (18 patients), or college and above (11 patients) education levels. In the control group, there were 26 males and 16 females who were aged 21–69 years (mean, 47.61 ± 11.95 years). The causes of injury in the control group included traffic accidents (18 cases), falls from heights (14 cases), heavy object trauma (7 cases), and others (3 cases). The highest education levels of control-group patients were primary school (11 patients), junior high and high school (21 patients), and college and above (10 patients). The clinical data regarding sex, age, cause of injury, and educational level were not significantly different between the two groups (\( P > 0.05 \)).

Between-group comparison of emergency care
Pre-hospital emergency response time, consultation time, imaging reporting time, and test reporting time values determined for the study group were shorter than those for the control group (\( P < 0.05 \)), as shown in Table 1.

Between-group inflammatory stress response indicator level comparisons, pre- and post-intervention
Pre-intervention serum IL-6 (78.71 ± 27.59 pg/mL), CRP (19.80 ± 6.77 mg/L), and PCT (3.66 ± 1.82 ng/mL) levels in the study group were not significantly different from those of the control group (81.31 ± 32.11 pg/mL, 21.29 ± 8.02 mg/L, 3.95 ± 2.11 ng/mL; \( P > 0.05 \)). However, the levels of serum indicators of both groups were lower post- vs pre-intervention. In the study group, post-intervention serum levels of IL-6 (17.35 ± 5.33 pg/mL), CRP (2.27 ± 0.56 mg/L), and PCT (0.22 ± 0.07 ng/mL) were lower than those in the control group (30.15 ± 12.38 pg/mL, 3.13 ± 0.77 mg/L, 0.38 ± 0.12 ng/mL; \( P < 0.05 \); Table 2).

Between-group complication rate comparison
The incidence of complications in the study group (9.52%) was lower than that in the control group (26.19%, \( P < 0.05 \); Table 3).

Between-group comparison of patient prognoses
The patient prognoses in the study group were better than those in the control group (\( P < 0.05 \), Table 4).
<table>
<thead>
<tr>
<th>Table 1 Comparison of emergency care between the two groups (mean ± SD, min)</th>
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<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>Study Group</td>
</tr>
<tr>
<td>Control group</td>
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<tr>
<td><em>t</em> value</td>
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<td><em>P</em> value</td>
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<tr>
<th>Table 2 Comparison of the levels of inflammatory stress indicators before and after the intervention in the two groups (mean ± SD)</th>
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<tbody>
<tr>
<td><strong>Group</strong></td>
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<tr>
<td><strong>Pre-intervention</strong></td>
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<tr>
<td>Study Group</td>
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<td>Control group</td>
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<td><em>t</em> value</td>
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IL-6: Interleukin-6; CRP: C-reactive protein; PCT: Procalcitonin.

<table>
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<tr>
<th>Table 3 Comparison of complication rates between the two groups, n (%)</th>
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<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>Study Group</td>
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<tr>
<td>Control group</td>
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<tr>
<td><em>χ²</em> value</td>
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<td><em>P</em> value</td>
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<tr>
<th>Table 4 Comparison of the prognosis of the two groups, n (%)</th>
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<tr>
<td><strong>Group</strong></td>
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Between-group comparison of nursing satisfaction

In the study group, satisfaction with nursing care was higher (95.24%) than in the control group (78.57%, *P* < 0.05; Table 5).

**DISCUSSION**

Craniofacial injuries are critical conditions caused by external violence, and are associated with a high rate of disability and death due to the potential effects on the central nervous system[10,11]. Due to the critical nature and rapid progression of craniofacial injuries, it is important to intervene early with effective care plans[12].
Table 5 Comparison of nursing satisfaction between the two groups, n (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Highly satisfied</th>
<th>Fairly satisfied</th>
<th>Unsatisfied</th>
<th>Satisfaction with the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>42</td>
<td>29 (69.05)</td>
<td>11 (26.19)</td>
<td>2 (4.76)</td>
<td>40 (95.24)</td>
</tr>
<tr>
<td>Control group</td>
<td>42</td>
<td>21 (50.00)</td>
<td>12 (28.57)</td>
<td>9 (21.43)</td>
<td>33 (78.57)</td>
</tr>
</tbody>
</table>

χ² value 5.126, P value 0.024

When the traditional model of care is employed, nursing staff tend to passively implement relevant interventions in accordance with departmental requirements and disease commonalities. Therefore, the traditional model fails to address issues in a systematic and timely manner, making it difficult for patients to benefit from the treatment provided[13,14]. FMEA is an important clinical quality management model that integrates root cause analysis, hazard analysis and critical control points, failure modes, and effects analysis to quantitatively and prospectively assess possible process failures, identify factors contributing to and the effects of failures, and develop practical solutions for failures in accordance with findings[15]. This study used a FMEA-based method to reveal the severity or likelihood of emergency care delays. As a result, screening of high-risk aspects of care could be performed, and intervention plans could be assessed to ensure treatment improvement. Potential factors leading to failure may also be explored. Further, the medical resources available via management support, divisions of responsibilities, management strategies, and action strategies can also be used to optimize and implement intervention strategies. These strategies have the potential to improve the quality of medical services[16,17].

The present study findings showed that the pre-hospital emergency responses, consultations, and imaging and test report delivery times were shorter for patients in the study group than for those in the control group. Further, the prognoses of patients in the study group were better than those of the patients in the control group. Study group levels of serum IL-6, CRP, and PCT were lower than those in the control group (P < 0.05), confirming the value of FMEA-based emergency management in patients with craniocerebral damage. The implementation of the FMEA-based strategy shortened the time spent on diagnosis and treatment, better controlled the degree of inflammatory stress experienced, reduced the complication risks, and promoted disease regression compared with the traditional model. FMEA-based strategy implementation also shortened the time the patients spent in the clinic, controlled their inflammatory stress indicator levels, reduced complication risk, and promoted good disease outcomes.

The FMEA-based model is an important tool for facilitating risk assessment, improving treatment, and managing the treatment process. The FMEA model is designed to prevent issues before they happen and continuously improve the quality of care by adjusting for process and system deficiencies. The strategy effectively exposes deficiencies and defects in process control and project management, and may be used to achieve standardized management strategies and improved care using the quantifiable indicator, RPN. The admission process used in traditional emergency care is cumbersome and complex, with the receiving nurse implementing admission placement only after admission to the department. The process relies on the provision of a bed, lacks good proactive reception, and results in low nursing efficiency. In contrast, FMEA-based emergency management has the potential to simplify admission procedures and open green channels, shortening the time needed to perform emergency care and ensure that patients are treated effectively and early[18,19]. In addition, in traditional emergency nursing management, nursing staff are encouraged to complete tasks in a mechanical manner when receiving patients, and their levels of active service consciousness and enthusiasm are low. In addition, some nursing staff lack professional knowledge and the ability to disseminate information, which has the potential to affect patient compliance to varying degrees. When using FMEA theory-based nursing management, job objectives are clear, promoting nursing staff attentiveness and responsibility. In this situation, the nursing staff have the ability to actively acquire needed professional knowledge within the department and improve their professional status, which is conducive to ensuring quality clinical nursing care[20].

The results of this study also showed that the study group patients had higher levels of satisfaction with their care than did those in the control group (P < 0.05), suggesting that FMEA-based emergency management is advantageous because it improves the
acceptance of care by patients with craniocerebral injuries. Patients treated in accordance with the FMEA theory are treated rapidly and effectively, which reduces disease-related complications and improves patient satisfaction. Some studies have also shown that the admission process used in conventional emergency care is complex, and the lack of integration between the various tasks during examination, transfer and treatment is often due to human or systematic factors, resulting in a poor patient experience. Using FMEA theory-based methods is conducive to enhancing patient trust in healthcare professionals, improving the healthcare experience, and increasing patient satisfaction with healthcare service enhancement[21,22].

CONCLUSION
In conclusion, FMEA-based emergency management of craniocerebral injury patients has the potential to effectively shorten the amount of time spent on emergency care, alleviate inflammatory stress, reduce the risk of complications, and improve patient prognoses, while also achieving high levels of patient satisfaction. However, the observation and study time of this study was relatively short. Therefore, whether patients with craniocerebral injuries can benefit from FEMA-based emergency management needs to be further explored and confirmed using extended clinical follow-ups.

ARTICLE HIGHLIGHTS

Research background
In recent years, traffic accidents and work-at-height injuries have increased, and the incidence of brain injuries caused by this has risen sharply.

Research motivation
Explore the application value of emergency management based on failure mode and impact analysis (FMEA) in the treatment of head injury.

Research objectives
This study aimed to explore the impact of emergency management based on FMEA on the treatment of head injury.

Research methods
A study was conducted on 84 patients with craniocerebral injury admitted to our hospital from November 2019 to March 2021.

Research results
For the study group, the evaluation parameters (pre-hospital emergency response time, consultation time, time required to report imaging results, and test report time) were shorter than those of the control group. After the intervention, the serum index levels of the two groups were lower than the pre-intervention level. Study The incidence of complications in the study group was lower than that of the control group. The prognosis of patients in the study group was better than that of the control group ($P < 0.05$). The nursing satisfaction of patients in the study group was higher than that of the control group.

Research conclusions
FMEA-based craniocerebral injury management effectively shortens the time spent on emergency care, reduces inflammatory stress and complication risk levels, and helps improve patient prognoses, while achieving high patient care satisfaction levels.

Research perspectives
Emergency management based on FMEA can be more widely used in the treatment of head injury.
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Observational Study

Predictive value of alarm symptoms in Rome IV irritable bowel syndrome: A multicenter cross-sectional study

Qian Yang, Zhong-Cao Wei, Na Liu, Yang-Lin Pan, Xiao-Sa Jiang, Xin-Xing Tantai, Qi Yang, Juan Yang, Jing-Jie Wang, Lei Shang, Qiang Lin, Cai-Lan Xiao, Jin-Hai Wang

ORCID number: Qian Yang 0000-0002-6563-7876; Zhong-Cao Wei 0000-0001-8931-680X; Na Liu 0000-0003-3246-9674; Yang-Lin Pan 0000-0002-7183-6716; Xiao-Sa Jiang 0000-0002-7121-8520; Xin-Xing Tantai 0000-0002-4105-6890; Qi Yang 0000-0001-5573-3031; Juan Yang 0000-0002-3193-5082; Jing-Jie Wang 0000-0001-7770-8232; Lei Shang 0000-0003-0470-0066; Qiang Lin 0000-0002-1105-3074; Cai-Lan Xiao 0000-0001-8476-5008; Jin-Hai Wang 0000-0003-1365-4727.

Author contributions: Qian Yang, Wang JH and Liu N concepted and designed the study; Yang Q, Wei ZC, Yang Q, Yang J, Wang JJ, Lin Q, Jiang XS and Xiao CL responsible for the acquisition of the data; Yang Q, Wei ZC, Shang L and Tantai XX involved in analysis and interpretation of data; Yang Q, Wang JH, Pan YL and Liu N drafted the manuscript and revised the article critically for important intellectual content; all authors have read and approved the final version of manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Xi’an Jiaotong University.

Abstract

BACKGROUND

Irritable bowel syndrome (IBS) is a common functional bowel disease that shares features with many organic diseases and cannot be accurately diagnosed by symptom-based criteria. Alarm symptoms have long been applied in the clinical diagnosis of IBS. However, no study has explored the predictive value of alarm symptoms in suspected IBS patients based on the latest Rome IV criteria.

AIM

To investigate the predictive value of alarm symptoms in suspected IBS patients based on the Rome IV criteria.

METHODS

In this multicenter cross-sectional study, we collected data from 730 suspected IBS patients evaluated at 3 tertiary care centers from August 2018 to August 2019. Patients with IBS-like symptoms who completed colonoscopy during the study
INTRODUCTION

As a functional bowel disease (FBD), irritable bowel syndrome (IBS) is characterized by recurrent abdominal pain with changes in bowel habits[1]. The most recent study showed that the prevalence of IBS is 4.6%[2] and ranges from 6.8% to 33.3% in Asia[3]. Although IBS does not directly increase mortality, it significantly affects patients' quality of life, the results in the waste of medical resources and increases social burden[4,5].

The diagnosis of IBS depends on symptom-based criteria. Due to a lack of reliable diagnostic tests and specific biomarkers and overlap between symptoms of IBS and those of multiple organic diseases, the accuracy of symptom-based criteria is poor in practical applications[6,7]. Guidelines and consensus[8-10] advocate positive diagno-
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P-Editor: Gong ZM

MATERIALS AND METHODS

Study population
This multicenter cross-sectional study was conducted at three academic urban tertiary care centers from August 2018 to August 2019. These were the Second Affiliated Hospital of Xi’an Jiaotong University, Tangdu Hospital of Air Force Medical University and the Affiliated Hospital of Northwest University (Xi’an No. 3 Hospital). Patients came to the centers with gastrointestinal symptoms, and they were initially evaluated and managed by gastroenterologists. Those with IBS-like symptoms who completed colonoscopy during the study period were identified by investigators through medical records. Then, investigators further called eligible patients to confirm whether they met the inclusion and exclusion criteria and whether they had completed a routine fecal exam, routine blood exam and fecal occult blood test. Patients who had undergone blood and stool tests within 6 mo were not re-examined. Otherwise, eligible patients were required to finish these tests. Detailed information on qualified candidates was obtained via telephone and a questionnaire (paper questionnaires were handed out face-to-face or sent as an electronic version via WeChat). Oral informed consent was acquired from all included patients. This study was approved by the ethics committee of the Second Affiliated Hospital of Xi’an Jiaotong University and registered at ClinicalTrials.gov (NCT 03620994).

Inclusion and exclusion criteria
Inclusion criteria: (1) The presence of IBS symptoms that met the Rome IV criteria; (2) Age 18 years old or older; (3) Visited the gastroenterology clinics and completed colonoscopy; and (4) A routine blood examination, routine fecal examination, and fecal occult blood test were performed within the last 6 mo (otherwise, eligible patients were required to finish these tests).

Exclusion criteria: (1) Other diagnosed diseases that can explain patients’ IBS symptoms; (2) Metabolic diseases (uncontrolled thyroid diseases and diabetes); (3) Severe neurological and psychiatric disorders; (4) Severe and unstable extraintestinal conditions; (5) History of major abdominal surgery; (6) Pregnancy, possible pregnancy or lactation; (7) Colonoscopy was performed in the past 6 mo; (8) Currently taking large doses of anti-anxiety/anti-depressant drugs or enteric sensitive antibiotics; (9) Malignancy diagnosed to be in an active state within the last year of enrollment (excluding completely resected localized basal cell or squamous cell carcinoma of the skin); or (10) Refusal to take part in the study (see Supplementary material for details).

Data collection
In this study, data were collected by designated researchers according to a specifically designed questionnaire. The main points included basic demographic characteristics, gastrointestinal symptoms, alarm symptoms, lifestyle habits, personal history, family history, medical expenses, psychological self-rating scale (self-rating anxiety scale, self-rating depression scale), laboratory results (routine fecal exam, routine blood exam and fecal occult blood test), colonoscopy findings and pathological results (if a biopsy was taken). Alarm symptoms included rectal bleeding, fecal occult blood [using the Fecal Occult Blood Test Kit (Colloidal Gold)], anemia, fever, nocturnal symptoms, unintended weight loss (in the last 3 mo), onset age > 50 years, and family history (CRC, inflammatory bowel disease (IBD) and celiac disease)[1,13-15]. With regard to organic diseases, we only included lesions that may explain IBS symptoms, and the results of colonoscopy and pathology were the gold standard. If not obstructive, colorectal polyps, melanosis coli, colonic diverticulum without inflammation, rectal...
varices, colic cyst, colonic leiomyoma, lipoma and neuroendocrine tumor, hemorrhoids, and anal fissures were identified as nonorganic diseases.

**Rome IV criteria for IBS**

Suspected IBS patients were those with IBS-like symptoms according to the Rome IV criteria, i.e., recurrent abdominal pain occurring, on average, at least 1 day a week in the last 3 months and associated with 2 or more of the following criteria: defecation, a change in stool frequency, or a change in the form (appearance) of the stool. Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis. In this study, patients with IBS-like symptoms and no organic diseases found by colonoscopy were defined as the IBS group.

**Colonoscopy and pathology examination**

In this study, all subjects signed an informed consent form for colonoscopy. Before undergoing colonoscopy, the patients were required to take 3000 mL of pegylated electrolyte powder in batches for bowel preparation. Colonoscopy was performed independently by experienced endoscopy operators who remained blinded to other patient information. The operators took biopsies when necessary according to endoscopic findings. When colorectal mucosa appeared normal, random biopsy was generally not performed. The pathologists also evaluated the specimens and made a pathological diagnosis without knowing other information about each patient.

**Statistical analysis**

In this study, quantitative variables are presented as the mean ± SD, and qualitative variables are expressed as percentages. Univariate analysis was performed using the chi-square test or Fisher’s exact test when appropriate. Multivariate logistic regression analysis (forward stepwise) was used to explore the independent risk factors for organic diseases, and the results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). The positive predictive value (PPV) and missed diagnosis rate were calculated to evaluate the predictive value of alarm symptoms. Statistical analyses were performed using SPSS 18.0 (SPSS Inc. Chicago, IL, United States) software. Double-tailed \( P < 0.05 \) values were considered statistically significant.

**RESULTS**

**Subject characteristics**

In this study, 945 patients were identified in the initial screening; of these, 89 were not successfully contacted, and 126 did not meet the eligibility criteria. Finally, a total of 730 patients were enrolled (Figure 1). With the exception of the psychological self-rating scale, which was completed by only 328 patients, all other data for the 730 patients were obtained and included in the data analysis. According to the colonoscopy and pathology results, suspected IBS patients were divided into the IBS group (n = 654) and the organic disease group (n = 76).

Univariate analysis showed that marital status (\( P = 0.014 \)) was significantly different between the two groups. However, there were no significant differences in gender, body mass index, educational level, alcohol use, tobacco use, exercise time, history of gastrointestinal infection, sleep quality, dietary factors, psychological self-rating scale or medical expenses (\( P > 0.05 \)) (Table 1).

**Predictive value of alarm symptoms**

The incidence of alarm symptoms in suspected IBS patients was as high as 75.34%. Univariate analysis indicated that fecal occult blood (\( P = 0.003 \)), anemia (\( P = 0.007 \)) and unintended weight loss (\( P = 0.003 \)) were associated with significant differences (Table 1). All factors in Table 1, except the psychological self-rating scale (which only 328 patients completed), were included in the logistic regression analysis. The results showed that female sex [OR = 0.560 (95% CI: 0.330-0.949), \( P = 0.031 \)], marital status (\( P = 0.030 \)), anemia [OR = 2.825 (95% CI: 1.273-6.267), \( P = 0.011 \)], fecal occult blood [OR = 1.940 (95% CI: 1.041-3.613), \( P = 0.037 \)] and unintended weight loss (\( P = 0.009 \)) were independently associated with organic diseases (Table 2). In addition, there was a significant difference in the prevalence of organic disease when the number of alarm symptoms varied (\( P = 0.013 \)) (Table 3).

In this study, colonoscopy was used as the gold standard, and patients with a normal colonoscopy were identified as having IBS. Patients with one or more alarm symptoms were considered to have organic diseases.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IBS (n = 654)</th>
<th>Organic disease (n = 76)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>307 (46.94)</td>
<td>27 (35.53)</td>
<td>0.059</td>
</tr>
<tr>
<td>Onset age (yr)</td>
<td></td>
<td></td>
<td>0.682</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>268 (40.98)</td>
<td>33 (43.42)</td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>386 (59.02)</td>
<td>43 (56.58)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td></td>
<td></td>
<td>0.360</td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>37 (5.66)</td>
<td>1 (1.32)</td>
<td></td>
</tr>
<tr>
<td>18.5-23.9</td>
<td>337 (51.59)</td>
<td>45 (59.21)</td>
<td></td>
</tr>
<tr>
<td>24.0-27.9</td>
<td>212 (32.42)</td>
<td>26 (34.21)</td>
<td></td>
</tr>
<tr>
<td>≥ 28</td>
<td>48 (7.34)</td>
<td>4 (5.26)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td>Married</td>
<td>592 (90.52)</td>
<td>60 (78.95)</td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>46 (7.03)</td>
<td>11 (14.47)</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>3 (0.46)</td>
<td>1 (1.32)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>13 (1.99)</td>
<td>4 (5.26)</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td>0.446</td>
</tr>
<tr>
<td>Elementary</td>
<td>88 (13.46)</td>
<td>13 (17.11)</td>
<td></td>
</tr>
<tr>
<td>Junior high school</td>
<td>176 (26.91)</td>
<td>14 (18.42)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>153 (23.39)</td>
<td>19 (25.00)</td>
<td></td>
</tr>
<tr>
<td>University or technical college</td>
<td>218 (33.33)</td>
<td>29 (30.86)</td>
<td></td>
</tr>
<tr>
<td>Postgraduate</td>
<td>19 (2.91)</td>
<td>1 (1.32)</td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td>0.394</td>
</tr>
<tr>
<td>Almost not</td>
<td>488 (74.62)</td>
<td>52 (68.42)</td>
<td></td>
</tr>
<tr>
<td>Previous</td>
<td>45 (6.88)</td>
<td>5 (6.58)</td>
<td></td>
</tr>
<tr>
<td>At present</td>
<td>121 (18.50)</td>
<td>19 (25.00)</td>
<td></td>
</tr>
<tr>
<td>Tobacco use</td>
<td></td>
<td></td>
<td>0.102</td>
</tr>
<tr>
<td>Almost not</td>
<td>456 (69.72)</td>
<td>44 (57.89)</td>
<td></td>
</tr>
<tr>
<td>Previous</td>
<td>49 (7.49)</td>
<td>7 (9.21)</td>
<td></td>
</tr>
<tr>
<td>At present</td>
<td>149 (22.78)</td>
<td>25 (32.89)</td>
<td></td>
</tr>
<tr>
<td>Exercise time</td>
<td></td>
<td></td>
<td>0.406</td>
</tr>
<tr>
<td>&lt; 0.5 h/d</td>
<td>154 (23.35)</td>
<td>24 (31.58)</td>
<td></td>
</tr>
<tr>
<td>≥ 0.5 h/d</td>
<td>183 (27.98)</td>
<td>21 (27.63)</td>
<td></td>
</tr>
<tr>
<td>≥ 1 h/d</td>
<td>139 (21.25)</td>
<td>12 (17.11)</td>
<td></td>
</tr>
<tr>
<td>≥ 2 h/d</td>
<td>178 (27.22)</td>
<td>19 (25.00)</td>
<td></td>
</tr>
<tr>
<td>History of GI infection</td>
<td>72 (11.01)</td>
<td>6 (7.89)</td>
<td>0.405</td>
</tr>
<tr>
<td>Poor sleep quality</td>
<td>236 (36.09)</td>
<td>26 (34.21)</td>
<td>0.747</td>
</tr>
<tr>
<td>Dietary factor</td>
<td></td>
<td></td>
<td>0.900</td>
</tr>
<tr>
<td>Raw or cold food</td>
<td>131 (20.03)</td>
<td>17 (22.37)</td>
<td></td>
</tr>
<tr>
<td>Spicy food</td>
<td>258 (39.45)</td>
<td>37 (48.68)</td>
<td></td>
</tr>
<tr>
<td>Lipid food</td>
<td>119 (18.20)</td>
<td>18 (23.68)</td>
<td></td>
</tr>
<tr>
<td>Milk and dairy products</td>
<td>95 (14.53)</td>
<td>9 (11.84)</td>
<td></td>
</tr>
<tr>
<td>Animal protein</td>
<td>32 (4.89)</td>
<td>4 (5.26)</td>
<td></td>
</tr>
</tbody>
</table>
Symptoms were predicted to have organic disease, and those without alarm symptoms were predicted to have IBS. As shown in Table 4, the PPV for organic disease in suspected IBS patients with alarm symptoms was calculated. The PPVs of individual alarm symptoms for organic disease ranged from 5% to 30% and decreased from high to low as follows: anemia (22.92%), fecal occult blood (19.35%), unintended weight loss (16.48%), rectal bleeding (14.81%), onset age > 50 years (10.96%), nocturnal symptoms (9.39%), family history of CRC, IBD or celiac disease (8.33%) and fever (5.56%). The PPVs of anemia combined with fecal occult blood, anemia combined with unintended weight loss, and fecal occult blood combined with unintended weight loss were 69.23%, 38.89% and 30.00%, respectively. The PPV was 100% when anemia, fecal occult blood and unintended weight loss were combined. As shown in Table 5, the PPV of symptom-based criteria (Rome IV) in diagnosing IBS was calculated with and without considering alarm symptoms. The PPV of Rome IV for diagnosing IBS was 89.59% without considering alarm symptoms; the PPV and missed diagnosis rate were 91.67%
Table 2 Multivariate analysis for clinical factors and alarm symptoms

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OR (95%CI)</th>
<th>P value</th>
<th>Partial regression coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (ref male)</td>
<td>0.560 (0.330, 0.949)</td>
<td>0.031</td>
<td>-0.580</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>2.499 (1.199, 5.209)</td>
<td>0.015</td>
<td>0.916</td>
</tr>
<tr>
<td>Divorced</td>
<td>1.184 (0.088,15.956)</td>
<td>0.899</td>
<td>0.169</td>
</tr>
<tr>
<td>Widowed</td>
<td>3.260 (0.964,11.029)</td>
<td>0.057</td>
<td>1.182</td>
</tr>
<tr>
<td>Anemia (ref absence)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fecal occult blood (ref absence)</td>
<td>1.940 (1.041, 3.613)</td>
<td>0.037</td>
<td>0.663</td>
</tr>
<tr>
<td>Unintended weight loss (kg) ²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2.5</td>
<td>2.389 (1.255, 4.548)</td>
<td>0.008</td>
<td>0.871</td>
</tr>
<tr>
<td>2.5-5.0</td>
<td>1.868 (0.751, 4.642)</td>
<td>0.179</td>
<td>0.625</td>
</tr>
<tr>
<td>5.0-7.5</td>
<td>0.904 (0.263, 3.110)</td>
<td>0.872</td>
<td>-0.101</td>
</tr>
<tr>
<td>≥ 7.5</td>
<td>8.027 (1.638,39.335)</td>
<td>0.010</td>
<td>2.083</td>
</tr>
</tbody>
</table>

¹All factors in Table 1, except the psychological self-rating scale were included in the logistic regression analysis.
²Referred to weight loss in the last 3 mo. CI: Confidence interval; OR: Odds ratio.

Table 3 Prevalence of organic disease according to number of alarm symptoms

<table>
<thead>
<tr>
<th>Number of alarm symptoms</th>
<th>Number of patients (n = 730)</th>
<th>Patients with organic disease, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>180</td>
<td>15 (8.33)</td>
<td>0.013</td>
</tr>
<tr>
<td>1</td>
<td>250</td>
<td>21 (8.40)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>20 (11.11)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>91</td>
<td>12 (13.19)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>2 (10.53)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>3 (42.86)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>2 (66.67)</td>
<td></td>
</tr>
</tbody>
</table>

and 74.77% when all alarm symptoms were combined with Rome IV and 92.09% and 34.10% when only fecal occult blood, unintended weight loss and anemia were combined with Rome IV.

Organic diseases
The prevalence of organic disease was 10.41% in suspected IBS patients. The most common lesion was non-IBD and noninfectious colitis (a significant colonoscopic finding indicative of inflammation, differentiated from IBD and infectious colitis [16]) (n = 42, 5.75%), followed by terminal ileitis (n = 18, 2.47%), CRC (n = 11, 1.51%), and ulcerative colitis (n = 8, 1.10%) (Table 6). We also randomly collected colonoscopy findings of 725 healthy examiners who went to the physical examination centers in the same period. The prevalence of terminal ileitis, CRC, ulcerative colitis and total organic disease were higher in suspected IBS patients than in healthy examiners (P < 0.05) (Supplementary Table 1).

DISCUSSION
Alarm symptoms are common in IBS patients, but not all alarm symptoms have good predictive value for organic disease[13]. Hammer et al[6] suggested that onset age > 50
Table 4 Utility of alarm symptoms for identifying organic disease

<table>
<thead>
<tr>
<th>Alarm symptoms</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset age &gt; 50 yr</td>
<td>10.96</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>14.81</td>
</tr>
<tr>
<td>Fecal occult blood</td>
<td>19.35</td>
</tr>
<tr>
<td>Unintended weight loss $^1$</td>
<td>16.48</td>
</tr>
<tr>
<td>Anemia</td>
<td>22.92</td>
</tr>
<tr>
<td>Fever</td>
<td>5.56</td>
</tr>
<tr>
<td>Nocturnal symptoms</td>
<td>9.39</td>
</tr>
<tr>
<td>Family history of IBD, CRC or celiac disease</td>
<td>8.33</td>
</tr>
<tr>
<td>Anemia + fecal occult blood</td>
<td>69.23</td>
</tr>
<tr>
<td>Anemia + unintended weight loss</td>
<td>38.89</td>
</tr>
<tr>
<td>Fecal occult blood + unintended weight loss</td>
<td>30.00</td>
</tr>
<tr>
<td>Anemia + fecal occult blood + unintended weight loss</td>
<td>100.00</td>
</tr>
</tbody>
</table>

$^1$Referred to weight loss in the last 3 mo. CRC: Colorectal cancer; IBD: Inflammatory bowel disease; PPV: Positive predictive value.

Table 5 The accuracy of alarm symptoms in diagnosing irritable bowel syndrome

<table>
<thead>
<tr>
<th>Colonoscopy findings</th>
<th>IBS</th>
<th>Organic disease</th>
<th>PPV (%)</th>
<th>Missed diagnosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without considering alarm symptoms</td>
<td>654</td>
<td>76</td>
<td>89.59</td>
<td></td>
</tr>
<tr>
<td>All alarm symptoms considered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence (predicted IBS)</td>
<td>165</td>
<td>15</td>
<td>91.67</td>
<td>74.77</td>
</tr>
<tr>
<td>Presence (predicted organic disease)</td>
<td>489</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certain alarm symptoms considered $^1$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence (predicted IBS)</td>
<td>431</td>
<td>37</td>
<td>92.09</td>
<td>34.10</td>
</tr>
<tr>
<td>Presence (predicted organic disease)</td>
<td>223</td>
<td>39</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$Referred to anemia, fecal occult blood and unintended weight loss. IBS: Irritable bowel syndrome; PPV: Positive predictive value.

Table 6 Colonoscopy findings in suspected irritable bowel syndrome patients

<table>
<thead>
<tr>
<th>Colonoscopy findings</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative colitis</td>
<td>8</td>
<td>1.10</td>
</tr>
<tr>
<td>Non-IBD and noninfectious colitis</td>
<td>42</td>
<td>5.75</td>
</tr>
<tr>
<td>CRC</td>
<td>11</td>
<td>1.51</td>
</tr>
<tr>
<td>Terminal ileitis</td>
<td>18</td>
<td>2.47</td>
</tr>
<tr>
<td>Total organic diseases</td>
<td>76</td>
<td>10.41</td>
</tr>
</tbody>
</table>

CRC: Colorectal cancer; IBD: Inflammatory bowel disease.

years and blood stains on toilet paper had good predictive value for organic disease. In China, one study$^{[17]}$ showed that onset age > 40 years, hemafecia, melena and anemia helped distinguish organic disease from functional disease, while another study$^{[18]}$ found that hematochezia, emaciation and anemia helped distinguish the two. However, both of these studies focused on patients with lower gastrointestinal
symptoms rather than suspected IBS patients. Based on the Rome IV criteria, we found that fecal occult blood, unintended weight loss and anemia had high predictive value for organic disease. Hemorrhoids were not regarded as organic disease, considering that their prevalence rate is as high as 50.28% in Chinese adults[19], which could affect the judgment of the value of rectal bleeding. In addition, the proportion of patients with organic disease increased as the number of alarm symptoms increased, consistent with previous studies[15].

Some studies[6,11,12] have shown that symptom-based criteria combined with alarm symptoms have high predictive value for diagnosing IBS. Vanner et al[11] found that the PPVs in prospective and retrospective studies were 98% and 100%, respectively. Whitehead et al[12] showed that the PPV was 47.9% without considering alarm symptoms and increased to 52.1% when considering alarm symptoms, with a missed diagnosis rate of 84%, and the PPV of individual alarm symptoms for identifying organic disease was 7%-9%. In this study, the PPV of Rome IV for diagnosing IBS was 89.59% when ignoring alarm symptoms and increased to 91.67% when all alarm symptoms were considered, with a missed diagnosis rate of 74.77%. When only fecal occult blood, unintended weight loss and anemia were considered, the PPV was 92.09%, but the missed diagnosis rate decreased to 34.10%. Furthermore, anemia, fecal occult blood and unintended weight loss alone had a higher PPV for organic disease, and the PPV for organic disease was 100% when anemia, fecal occult blood and unintended weight loss were combined.

These results indicate that for suspected IBS patients, considering alarm symptoms does not significantly improve PPV for diagnosing IBS. However, alarm symptoms can help identify patients with organic disease; in particular, fecal occult blood, unintended weight loss and anemia have a high value in predicting organic disease. The presence of those factors suggests that further examination may be needed, but they are not recommended as exclusion criteria for diagnosing IBS, consistent with the
findings of Whitehead et al[12], for several reasons. First, the prevalence of organic disease is relatively low, making the PPV of Rome IV criteria for diagnosing IBS high. As the incidence of alarm symptoms is high, the PPV is not significantly improved when considering all alarm symptoms, and the missed diagnosis rate is high. When only fecal occult blood, unintended weight loss and anemia are considered, the PPV remains high and almost unchanged, while the missed diagnosis rate decreases significantly. Second, a missed diagnosis of organic disease, such as IBD or CRC, has serious consequences[1]. However, a comprehensive diagnostic examination of all suspected IBS patients to exclude organic disease would place a huge burden on patients and society, especially given the expensive and invasive nature of colonoscopy[20]. Alarm symptoms have certain predictive value for organic disease. Evaluating the risk of organic disease individually by collecting alarm symptoms and other risk factors is an important part of the correct diagnosis of IBS and ensuring that high-risk patients (such as those with anemia, fecal occult blood and unintended weight loss) receive necessary tests and greater attention.

Some results of this study differ from those presented in previous studies. Reasons for these discrepancies include the following: (1) Hammer et al[6] evaluated all presenting patients and performed a full diagnostic workup for patients; Vanner et al [11] included only patients without alarm symptoms; Whitehead et al[12] conducted systematic chart reviews of patients with clinical diagnoses of IBS. In the above studies, the physician’s final diagnosis was the gold standard; (2) The diagnostic criteria for IBS and definitions of alarm symptoms vary among studies. We used the Rome IV criteria, while other studies used the Manning criteria and Rome I or Rome II criteria; and (3) The prevalence of organic disease, which could affect the assessment of predictive value, was 10.41% in this study, compared with 10.3% and 30.3% in previous studies[21,22]. Currently, there is no standard definition of organic disease that distinguishes it from IBS. The organic diseases in this study included ulcerative colitis, CRC, terminal ileitis, non-IBD and noninfectious colitis, which could explain IBS symptoms.

It has been suggested that not all symptoms should be attributed to IBS, which would delay colonoscopy[16,22]. Studies have also shown that a negative colonoscopy does not provide protection for IBS patients[23]. In this study, the prevalence of terminal ileitis, CRC and ulcerative colitis was significantly higher in suspected IBS patients than in healthy examiners. Although the prevalence of organic diseases is low, they incur a great deal of harm. Thus, a necessary colonoscopy should not be delayed in suspected IBS patients. The Chinese consensus recommends colonoscopy for patients aged over 40 years[9]. However, our results suggest that the predictive value of onset age is poor in suspected IBS patients. It is necessary to conduct more research based on IBS patients.

We also found that male sex (reference female) and never-married status were risk factors for organic disease. Studies have shown that females are more likely to have IBS[2]. The relationship between marital status and FBD may be related to differences in lifestyle and stress according to marital status[24].

One of the major advantages of this study is its large sample size. A total of 730 subjects were enrolled. Patients were evaluated independently by the receiving doctors. Colonoscopy and pathology were performed independently by operators without knowledge of other patient information, ensuring that the results were more consistent with the clinical reality. This is also the first study to explore the predictive value of alarm symptoms in suspected IBS patients based on the Rome IV criteria.

There were some limitations in this study. First, older patients are more likely to undergo colonoscopy, which may lead to a high incidence of alarm symptoms. However, the incidence of alarm symptoms in previous studies is similar to that in our study (70%-84%)[12,13,15]. Second, this study was mainly conducted in the form of questionnaires, which may have caused information bias. Third, due to the normal appearance of microscopic colitis under colonoscopy and because tests related to celiac disease, lactose malabsorption and bacterial overgrowth were not widely evaluated, we could not exclude the above diseases. However, the prevalence of these diseases is low in China. Finally, this study was conducted in 3 tertiary centers and limited to a northwest Chinese population. The findings deserve further validation in primary care units in gastrointestinal clinics and in national multicenters.

**CONCLUSION**

In conclusion, based on the Rome IV criteria, anemia, fecal occult blood and unin-
tended weight loss have high predictive value for organic disease in suspected IBS patients and can help identify patients who need further examination, but they are not recommended as exclusion criteria for diagnosing IBS. Moreover, a necessary colonoscopy should not be delayed.

ARTICLE HIGHLIGHTS

Research background
The diagnosis of irritable bowel syndrome (IBS) depends on symptoms, while the accuracy of symptom-based criteria is poor. Alarm symptoms have long been applied in the diagnosis of IBS. However, no study has explored the predictive value of alarm symptoms in suspected IBS patients based on the latest Rome IV criteria.

Research motivation
The symptoms of IBS overlap with those of many organic diseases, and IBS lacks specific diagnostic tests and biomarkers. There are differences in previous research results on the predictive value of alarm symptoms in IBS, and there is no relevant study based on Rome IV. Evaluating the value of alarm symptoms provides guidance for clinical evaluation of the risk of organic diseases in suspected IBS patients, giving necessary auxiliary examination and correct diagnosis of IBS.

Research objectives
The objective was to investigate the predictive value of alarm symptoms in suspected IBS patients based on Rome IV. Furthermore, an IBS prediction model was established to guide the clinical and scientific work of IBS.

Research methods
This cross-sectional study was conducted at three academic urban tertiary care centers to ensure the sample size, sample representativeness and reliability of the results. Eligible patients completed questionnaires (paper version or electronic version), underwent laboratory tests, and were assigned to the IBS or organic disease group according to colonoscopy findings and pathology results. Investigators did not give any intervention to the patients and inspectors, and the results were more in line with clinical practice.

Research results
Anemia, fecal occult blood, unintended weight loss, female sex and marital status were independently correlated with organic disease. The positive predictive value (PPV) of alarm symptoms for organic disease was highest for anemia, fecal occult blood and unintended weight loss, and it was 100% when these three factors were combined. The PPV and missed diagnosis rate for diagnosing IBS were 91.67% and 74.77% when all alarm symptoms were combined with Rome IV and 92.09% and 34.10% when only fecal occult blood, unintended weight loss and anemia were combined with Rome IV, respectively.

Research conclusions
Alarm symptoms, especially fecal occult blood, unintended weight loss and anemia, have a high predictive value for organic disease in suspected IBS patients based on Rome IV. The presence of those alarm symptoms suggests that further examination may be needed, but they are not recommended as exclusion criteria for diagnosing IBS.

Research perspectives
By collecting large-scale, high-quality and national multicenter data, a simple, practical and efficient IBS diagnosis model can be further constructed. Of course, we should continue to deepen the research on the etiology and mechanism of IBS, actively look for specific biomarkers and/or diagnostic tests and achieve a more accurate diagnosis of IBS.
REFERENCES


Prospective Study

5-min mindfulness audio induction alleviates psychological distress and sleep disorders in patients with COVID-19

Jing Li, Yun-Yun Zhang, Xiao-Yin Cong, Shu-Rong Ren, Xiao-Ming Tu, Jin-Feng Wu

Abstract

BACKGROUND
Mindfulness meditation is beneficial to mitigate the negative effects of the coronavirus disease 2019 (COVID-19) pandemic in the general population, but no study examined such meditation in the COVID-19 patients themselves.

AIM
To explore the short-term efficacy of mindfulness meditation in alleviating psychological distress and sleep disorders in patients with COVID-19.

METHODS
This prospective study enrolled patients with mild COVID-19 treated at Wuhan Fangcang Hospital in February 2020. The patients were voluntarily divided into either a mindfulness or a conventional intervention group. The patients were evaluated before/after the intervention using the Short Inventory of Mindfulness Capability (SMI-C), Hospital Anxiety and Depression Scale (HADS), and Pittsburgh Sleep Quality Index (PSQI).

RESULTS
Seventy-five participants were enrolled in this study, with 43 and 32 in the mindfulness and conventional groups, respectively. Before the intervention, there were no differences in SMI-C, HADS, or PSQI scores between the two groups. After the 2-wk intervention, the mindfulness level (from 30.16 ± 5.58 to 35.23 ± 5.95, P < 0.001) and sleep quality (from 12.85 ± 3.06 to 9.44 ± 3.86, P < 0.001) were significantly increased in the mindfulness group. There were no differences in the conventional group. After the intervention, the mindfulness level (35.23 ± 5.95 vs
Mindfulness meditation might be beneficial to alleviate psychological distress and sleep disorders in patients with COVID-19. In Wuhan, the hardest-hit area of COVID-19, the residents are prone to psychological problems, especially for nurses who play critical roles in public health emergencies. For patients with COVID-19, fear of the disease and negative emotions easily lead to a psychological crisis, and timely and effective psychological interventions are of great significance. Therefore, this study aimed to explore the efficacy of mindfulness meditation in alleviating psychological distress and sleep disorders in patients with COVID-19 in Wuhan Fangcang Hospital. Mindfulness meditation might be beneficial to alleviate negative emotions and improve sleep quality in patients with COVID-19.
MATERIALS AND METHODS

Study design and subjects
This prospective study enrolled patients with mild COVID-19 treated at Wuhan Fangcang Hospital in February 2020. This study was approved by the ethics review board of Jiangsu Province Hospital. Written informed consent was obtained from each participant.

The inclusion criteria were: (1) Patients with COVID-19 treated at Wuhan Fangcang Hospital; (2) 18-60 years of age and normal hearing, reading, and language; and (3) No history of mental diseases, and clear verbal expression. All participants enrolled in this study were diagnosed according to World Health Organization interim guidance[27]. The exclusion criteria were: (1) Concurrent with comorbidities of vital organs; (2) Receiving other psychological interventions; or (3) History of mental diseases (e.g., schizophrenia).

Groups
The intervention was explained to each potential participant in detail. According to their wishes, the participants were divided into either a mindfulness or a conventional intervention group. There was no blinding.

Interventions
The participants in both groups were treated with the same supportive therapy for COVID-19.

In the conventional group, the participants received conventional care/education about admission, COVID-19, medication, physical examinations, psychological support, and safety education.

Mindfulness meditation induction and mindfulness-based cognitive therapy (MBCT) were applied in the mindfulness intervention group. A 5-min mindfulness audio file produced by Li et al.[28] was played using a mobile phone through WeChat. The participants were guided into mindfulness meditation according to the instructions in the audio file. During mindfulness meditation, the participants were asked to keep an alert and relaxed posture, with the eyes gently closed. At least 1 h of collective Q&A was performed in the participants each day, and face-to-face psychological support was provided if necessary. The research group included one registered psychiatrist and three registered nurses with a bachelor’s degree or above and at least 3 years of working experience. The psychiatrist was responsible for selecting the 5-min mindfulness audio instructions and for training the nurses about mindfulness knowledge and nursing precautions before and after playing the mindfulness instructions. A WeChat group was generated for the participants during the study period. On the first day of participation, the mindfulness meditation audio and texts were pushed via WeChat. The nurses guided the participants to meditate, and the induction lasted about 30 min. On the second day, after mastering the mindfulness meditation training methods, the participants were free to undergo a daily mindfulness meditation (5-20 min) before sleeping. The nurses directed and supervised the daily mindfulness meditation and recorded the sleep quality of the participants.

Outcomes
The Short Inventory of Mindfulness Capability (SIM-C) was used to assess the mindfulness level of the participants[29] using 12 items in three categories (i.e., acting with awareness, describing, and non-judging of experience). The SIM-C scores were determined using a 5-point Likert scale, ranging from 1 (never true) to 5 (always true). A higher SIM-C score indicates a higher level of mindfulness.

The Hospital Anxiety and Depression Scale (HADS) was used to determine the levels of anxiety and depression in the participants[30] using seven items in two categories. Each item is weighed on a scale of 0-3. The total HADS score ranges from 0 to 21. A higher score indicates more severe anxiety or depression. HADS scores ranging from 9 to 21 indicate that a person is experiencing anxiety or depression.

The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality[31] using 18 items and seven components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction). Each item is weighed on four-interval scales (0-3). The total PSQI score ranges from 0 to 21, where higher scores indicate worse sleep quality. Sleep disorders were determined with PSQI > 7. The patients were evaluated using SIM-C, HADS, and PSQI before and after the intervention.
**Data collection**
Demographic characteristics (including age, sex, body weight, height, and educational background) and SIM-C, HADS, and PSQI scores were recorded.

**Statistical analysis**
SPSS 19.0 (IBM, Armonk, NY, United States) was used for statistical analyses. Continuous data are expressed as the mean ± SD. Differences between groups were analyzed using the independent-sample t test. Differences before and after the intervention were analyzed using the paired-sample t test. Categorical data are presented as n (%) and were analyzed using the chi-square test. Two-sided P values < 0.05 were considered statistically significant.

**RESULTS**

**Characteristics of the participants**
Figure 1 presents the flowchart of the participant enrollment process. In the mindfulness group, there were 30 males and 13 females; the participants were 42.23 ± 9.78 (range: 30-55) years of age. Eighteen males and fourteen females were enrolled in the conventional group; they were 44.35 ± 10.61 (range: 27-56) years of age (Table 1). There were no significant differences in SIM-C, HADS, or PSQI scores between the two groups before the intervention (P > 0.05; Tables 2 and 3).

**Mindfulness levels after intervention in patients with COVID-19**
After the 2-wk intervention, the mindfulness level (from 30.16 ± 5.58 to 35.23 ± 5.95, P < 0.001) was significantly increased in the mindfulness group and was significantly higher in the mindfulness group than in the conventional group (35.23 ± 5.95 vs 31.17 ± 6.50, P = 0.006; Tables 2 and 3).

**Sleep quality after the intervention**
After the 2-wk intervention, sleep quality (from 12.85 ± 3.06 to 9.44 ± 3.86, P < 0.001) in the mindfulness group was significantly improved, but there was no change in the conventional group. The sleep quality (9.44 ± 3.86 vs 11.87 ± 4.06, P = 0.011) was significantly higher in the mindfulness group than in the conventional group, and the degree of sleep quality (P = 0.022) was significantly different between the two groups (Tables 2 and 3).

**Anxiety and depression before and after the intervention**
Before the intervention, the participants in both groups experienced anxiety and depression. After the 2-wk intervention, the depression level was decreased significantly in the mindfulness group (from 14.15 ± 3.21 to 12.50 ± 4.01, P = 0.038), but there was no change in the conventional group. There were no significant differences in anxiety (P = 0.649) or depression (P = 0.263) between the two groups after the intervention (Tables 2 and 3).

**DISCUSSION**
COVID-19 damages physical health and poses a huge impact on mental health because of the isolation, uncertainty about disease outcomes, and rumors, leading to anxiety, depression, and negative emotions during treatment[10-12]. Therefore, timely and effective psychological counseling should be implemented in the comprehensive therapy of COVID-19[10-12,32]. A strongly effective intervention is necessary to relieve the overwhelming negative emotions, thus decreasing ego depletion[33]. Mindfulness meditation is a unique practice to enhance attention and awareness, focusing on one’s internal and external experiences in a moment of conscious and non-judgmental awareness[13-16,33]. Mindfulness is conducive to the treatment of a variety of conditions[13-16]. It also helps to regulate emotions and enhances well-being. Furthermore, mindfulness can reduce unconscious behaviors and overcome automaticity [13-16,34]. Mindfulness meditation is beneficial to mitigate the negative effects of the COVID-19 pandemic in the general population[23-26], but no study examined such meditation in the COVID-19 patients themselves. Therefore, this study aimed to explore the efficacy of mindfulness meditation in alleviating psychological distress.
Table 1 Baseline characteristics of patients with coronavirus disease 2019

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mindfulness group (n = 43)</th>
<th>Conventional group (n = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr (mean ± SD)</td>
<td>42.23 ± 9.78</td>
<td>44.35 ± 10.61</td>
<td>0.069</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (69.8)</td>
<td>18 (56.2)</td>
<td>0.228</td>
</tr>
<tr>
<td>Female</td>
<td>13 (30.2)</td>
<td>14 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Height, cm (mean ± SD)</td>
<td>169.51 ± 8.13</td>
<td>165.41 ± 8.46</td>
<td>0.037</td>
</tr>
<tr>
<td>Weight, kg (mean ± SD)</td>
<td>70.37 ± 12.52</td>
<td>64.97 ± 9.43</td>
<td>0.044</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td>0.345</td>
</tr>
<tr>
<td>Junior diploma or below</td>
<td>6 (14.0)</td>
<td>7 (21.9)</td>
<td></td>
</tr>
<tr>
<td>High and technical secondary school diploma</td>
<td>9 (20.9)</td>
<td>7 (21.9)</td>
<td></td>
</tr>
<tr>
<td>Junior college</td>
<td>9 (20.9)</td>
<td>10 (31.3)</td>
<td></td>
</tr>
<tr>
<td>Bachelor degree or above</td>
<td>19 (44.2)</td>
<td>8 (25.0)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Short Inventory of Mindfulness Capability, Hospital Anxiety and Depression Scale, and Pittsburgh Sleep Quality Index scores before and after intervention in patients with coronavirus disease 2019 between groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mindfulness group (n = 43)</th>
<th>Conventional group (n = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mindfulness (mean ± SD)</td>
<td>30.16 ± 5.58</td>
<td>29.42 ± 6.03</td>
<td>0.585</td>
</tr>
<tr>
<td>Anxiety (mean ± SD)</td>
<td>14.05 ± 2.56</td>
<td>13.60 ± 2.93</td>
<td>0.481</td>
</tr>
<tr>
<td>Depression (mean ± SD)</td>
<td>14.15 ± 3.21</td>
<td>14.00 ± 2.97</td>
<td>0.837</td>
</tr>
<tr>
<td>Sleep quality (mean ± SD)</td>
<td>12.85 ± 3.06</td>
<td>13.36 ± 4.12</td>
<td>0.572</td>
</tr>
<tr>
<td>After intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mindfulness (mean ± SD)</td>
<td>35.23 ± 5.95&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31.17 ± 6.50</td>
<td>0.006</td>
</tr>
<tr>
<td>Anxiety (mean ± SD)</td>
<td>12.91 ± 3.42</td>
<td>13.25 ± 2.83</td>
<td>0.649</td>
</tr>
<tr>
<td>Depression (mean ± SD)</td>
<td>12.50 ± 4.01</td>
<td>13.52 ± 3.68</td>
<td>0.263</td>
</tr>
<tr>
<td>Sleep quality (mean ± SD)</td>
<td>9.44 ± 3.86&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.87 ± 4.06</td>
<td>0.011</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05 vs before intervention in the mindfulness group.
<sup>b</sup>P < 0.001 vs before intervention in the mindfulness group.

Table 3 Short Inventory of Mindfulness Capability, Hospital Anxiety and Depression Scale, and Pittsburgh Sleep Quality Index scores before and after intervention in patients with coronavirus disease 2019 within groups

<table>
<thead>
<tr>
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<th>Mindfulness (n = 43)</th>
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</tr>
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<tr>
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and sleep disorders in patients with COVID-19. The results suggested that a short-term (2-wk) mindfulness induction can increase the mindfulness level, improve the sleep quality, and decrease the depression of patients with COVID-19.

The Wuhan Fangcang Hospital is a temporary hospital constructed to treat COVID-19 and has relatively crude facilities. Wuhan Fangcang Hospital has 1000 beds to isolate patients with COVID-19. A narrow space, a brightly lit environment, and strict
protective measures (e.g., masks and protective clothing) enhance negative emotions. This hospital serves public health purposes in terms of physical care and isolation on the patients, but the environment is not conducive to mitigating stress and anxiety. In this hospital and this study, a short-term mindfulness meditation audio file that only takes 15-20 min could significantly enhance the patients’ mindfulness by eliminating distractions and focusing on the current awareness.

Fear in response to life-threatening events is common in human beings[35,36]. An effective psychological intervention can elevate mindfulness levels, thereby offering the patient a positive attitude towards diseases. Mindfulness meditation originates from the ancient orient[37] and is closely related to activating the prefrontal lobe and the cingulate gyrus[34]. Mindfulness meditation brings a non-judgmental concentration on internal and external stimuli, and finally, a balanced mentality. Owing to the rapid spread of the epidemic, Wuhan was locked down on January 23, 2020. In the current situation, most patients with COVID-19 have a good prognosis[1,2], but fear remains[5-8,10-12]. In the present study, a 15-20 min mindfulness meditation was helpful for patients to foster positive emotions. This intervention can be performed together with the medical treatment of COVID-19. Mindfulness levels were significantly higher in the mindfulness intervention group than in the conventional group after the intervention, suggesting that the 15-20 min mindfulness meditation could effectively induce and enhance mindfulness in patients with COVID-19.

Anxiety and depression lead to sleep disorders, which, in turn, aggravate the negative emotions[38]. During the induction of the 5-min mindfulness meditation, the participants better controlled their emotions, cognitions, and behaviors. Davidson et al[39] reported that the left prefrontal cortex is significantly activated during meditation, and such activation is linked to the enhancement of positive emotions. Functional magnetic resonance imaging results suggested that mindfulness meditation can strengthen the insula’s function, change the brain’s circuit, and arouse more positive and optimistic feelings[13]. On the one hand, mindfulness meditation can guide the patients to focus on and get used to the current situation; on the other hand, it achieves a state of being mentally clear and emotionally calm, which improves sleep quality[40]. This study showed lower PSQI scores in the mindfulness group than in the conventional group after the intervention, indicating that an effective psychological intervention was as important as meditation in improving sleep quality.

At present, mindfulness-based stress reduction and MBCT can be combined with cognitive-behavioral therapy to provide a more definite psychological education about emotions, cognition, and functions[41]. In this study, the participants in both groups had high HADS scores before the intervention, indicating that the diagnosis and isolation influenced the psychological state of patients with COVID-19. After the 2-wk intervention, no significant difference in the HADS score was observed. Isolation and the cold environment of the hospital might play a role in this result, but it will have to be confirmed in future studies.

This study has some limitations. First, the participants were not randomized, and the assessors were not blinded. Second, the sample size was small, limiting the generalizability of the results. Additional studies are needed to address these issues.
CONCLUSION

In conclusion, a 5-min mindfulness meditation audio induction can elevate the mindfulness levels, improve the sleep quality, and decrease the depression in hospitalized patients with COVID-19. Furthermore, it is an effective, economical, and convenient non-drug psychological intervention that can be universally applied.

ARTICLE HIGHLIGHTS

Research background
At present, coronavirus disease 2019 (COVID-19) is becoming a severe public health concern, especially in Wuhan (China), the most hit area of COVID-19 infection in China, which has set up and opened nine Fangcang Hospitals to treat patients with COVID-19. For patients with COVID-19, fear of the disease and negative emotions easily lead to a psychological crisis, and a timely and effective psychological intervention is of great significance.

Research motivation
Mindfulness meditation is beneficial to mitigate the negative effects of the COVID-19 pandemic in the general population, but no study examined such meditation in the COVID-19 patients themselves.

Research objectives
The survey explored the efficacy of mindfulness meditation in alleviating psychological distress and sleep disorders in patients with COVID-19 in Wuhan Fangcang Hospital.

Research methods
This was a prospective study of patients with mild COVID-19 treated at Wuhan Fangcang Hospital in February 2020. The patients were voluntarily divided into either a mindfulness or a conventional group. The participants in both groups were treated with the same supportive therapy for COVID-19. Besides, the mindfulness group received mindfulness-based cognitive therapy, which contains a 5-min meditation.

Research results
After a 2-wk intervention, the mindfulness level (from 30.16 ± 5.58 to 35.23 ± 5.95, \( P < 0.001 \)) and sleep quality (from 12.85 ± 3.06 to 9.44 ± 3.86, \( P < 0.001 \)) significantly increased in the mindfulness group. However, there were no difference in the conventional group. After a 2-wk intervention, the mindfulness level (35.23 ± 5.95 vs 31.17 ± 6.50, \( P = 0.006 \)) and sleep quality (9.44 ± 3.86 vs 11.87 ± 4.06, \( P = 0.011 \)) were significantly increased in the mindfulness group than in the conventional group. Depression decreased in the mindfulness group (from 14.15 ± 3.21 to 12.50 ± 4.01, \( P = 0.038 \)), but there was no difference between the two groups.

Research conclusions
The short-term mindfulness meditation can increase the mindfulness level, improve the sleep quality, and decrease the depression of patients with COVID-19.

Research perspectives
The short-term mindfulness meditation is very useful to patients with COVID-19, and long-term mindfulness meditation is worth further study as well.

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Efficacy and safety of argatroban in treatment of acute ischemic stroke: A meta-analysis

Bin Lv, Fang-Fang Guo, Jia-Cai Lin, Feng Jing

ORCID number: Bin Lv 0000-0001-9858-8778; Fang-Fang Guo 0000-0001-8488-2917; Jia-Cai Lin 0000-0002-2921-7954; Feng Jing 0000-0002-3532-2013.

Author contributions: Lv B and Guo FF contributed equally to this work; Lv B and Guo FF searched the related articles, analyzed the data, and wrote the manuscript; Lin JC analyzed and interpreted the data; Jing F conceived and designed this study, and made critical revision to the manuscript; all the authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors deny any conflict of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: China

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report’s scientific

Abstract

BACKGROUND
Argatroban is a novel direct thrombin inhibitor that has been used for treatment of acute ischemic stroke (AIS). To our knowledge, no systematic analysis has assessed the efficacy and safety of argatroban for treatment of AIS.

AIM
To evaluate the efficacy and safety of argatroban for treatment of AIS.

METHODS
Cochrane Library, Medline, PubMed, and Web of Science were searched to retrieve all studies associated with argatroban and AIS. Effective rate, adverse events rate, and 95% confidence intervals were calculated and pooled using meta-analysis methodology.

RESULTS
We only found four randomized controlled studies, comprising 354 cases with 213 in the argatroban group and 141 in the control group. Great heterogeneity was found in the four studies ($\chi^2 = 11.44, P = 74\%$, $P = 0.01$). Subgroup analysis could not be performed because of the absence of detailed data. The two most recent studies showed acceptable heterogeneity ($\chi^2 = 1.56, P = 36\%, P = 0.21$). Our analysis showed that argatroban was not more effective than the control therapy in the acute phase of ischemic stroke ($Z = 0.01, P = 0.99$). Argatroban did not increase the risk of bleeding compared with the control group ($\chi^2 = 0.37, P = 0\%$, $P = 0.54$, $Z = 0.80$, $P = 0.42$).

CONCLUSION
Patients with AIS might not benefit from argatroban and combination therapy with argatroban does not increase bleeding tendency.

Key Words: Argatroban; Anticoagulation agents; Acute ischemic stroke; Thrombin; Thrombolysis; Meta-analysis

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Core Tip: This study is the first meta-analysis that systematically assessed the efficacy and safety of argatroban as a cure for acute ischemic stroke (AIS). The results showed that argatroban might not benefit for AIS. Also, this meta-analysis further suggested that argatroban does not increase the risk of bleeding for AIS.

INTRODUCTION

Acute ischemic stroke (AIS) is the most common type of cerebrovascular disease. Ischemic stroke (IS) is the leading cause of adult disability and has the second-highest fatality rate in the world[1]. Still, morbidity and mortality have shown a growing trend in recent years[2]. Evidence suggests that only aspirin and recombinant tissue-type plasminogen activator (r-tPA) have a definite curative effect on the acute phase of IS (Class A evidence, level I recommendation). The efficacy of other drugs is still lacking evidence-based support. Anticoagulant therapy has always been a focus in the field of AIS, but the results were controversial. Although anticoagulant therapy can reduce the recurrence of IS and the incidence of pulmonary embolism and deep vein thrombosis, its effect on the mortality and disability rate of IS is still unknown[3]. Also, anticoagulation increases the incidence of intracranial hemorrhage (ICH)[4]. So, traditionally used anticoagulant drugs, such as heparin, low molecular weight heparin, and warfarin are not recommended for AIS treatment. Argatroban is a novel, small-molecule, direct thrombin inhibitor. It exerts its anticoagulant function by binding with thrombin, not only in the state of dissolution but also in blood clotting[5]. It has been mainly proved for the treatment of thrombosis caused by heparin-induced thrombocytopenia. There is a growing body of evidence on the safety and efficiency of argatroban therapy for AIS[6-8]. In Japan and South Korea, argatroban therapy is also used in ischemic diseases including myocardial and cerebral ischemia[9]. However, there is still a lack of evidence for its efficacy and safety. To provide more reliable evidence for clinical practice, we conducted a Cochrane Collaboration systematic review that included the randomized controlled studies on AIS treatment using argatroban.

MATERIALS AND METHODS

Search strategy

A search of PubMed, Embase, Science Citation Index, Medline, and Cochrane Library was performed up to October 2020. The search was conducted using medical subject headings and keywords including “argatroban”, “4-methyl-1-(N(2)-(3-methyl-1,2,3,4-tetrahydro-8-quinolinesulfonyl)-L-arginyl)-2-piperidinecarboxylic acid”, “cerebral infarction”, “ischemic stroke”, “cerebrovascular disorder”, and “cerebrovascular accident”. Meanwhile, we retrieved references listed in studies and reviews researched from the online databases to obtain relevant data.

Selection criteria

We only enrolled randomized controlled studies that assessed the efficacy and safety...
of argatroban in treating AIS. All the studies were in English and published as full articles. Case reports, reviews, commentaries, editorials, and studies written in abstract form or published repeatedly were excluded to prevent homogeneity. The methodological quality of the included studies was assessed using the risk assessment tool for RCT bias in the Cochrane Systematic Reviewers’ Handbook.

**Outcome index**
The outcome and adverse effects were calculated from the data provided by the researchers. Validity and adverse effect assessment were based on the information synthesized from the studies. Validity mainly referred to therapeutic effect, assessed by neurological function scores. Adverse effects mainly referred to bleeding.

**Statistical analysis**
Relative risk ratio (RR) and 95% confidence interval (CI) were used as effect analysis statistics for categorical data. Efficiency and safety were calculated for all of the studies that were identified for the meta-analysis, and the results were combined using fixed- or random-effects modeling. Statistical heterogeneity was assessed using $\chi^2$ tests ($P < 0.05$ indicated statistical significance) and $P$ tests ($P < 0.05$, $P > 50\%$ indicated significant heterogeneity; $P > 0.05$, $P < 50\%$ indicated insignificant heterogeneity). The fixed-effects model was used if there was no statistical heterogeneity, otherwise, the random-effects model was used. Subgroup analyses were conducted for further investigation. Meta-analysis was conducted using RevMan version 5.4 (Cochrane collaboration), and $P < 0.05$ was defined as statistically significant.

**RESULTS**

**Description of the studies**
A total of 412 relevant studies were retrieved, and 408 were excluded because of duplication or failure to meet the inclusion criteria. Finally, four trials were included in our study[6,10-12]. The studies included 354 cases with 213 in the argatroban group and 141 in the control group. The literature screening process and results are showed in Figure 1. Two of the studies were conducted in North America and two in Japan. Three studies were multicenter and one was single center. The main characteristics of the included studies are presented in Table 1.

All four studies used improvement of neurological deficits to assess the efficiency of argatroban. The National Institutes of Health Stroke Scale, Modified Rankin Scale, Barthel Index, and activity in daily living were used in three studies. The evaluation method was not described in the other study[10]. Although there was no uniform standard, all the enrolled studies reported the effective rate of nerve function improvement, which was used to assess the efficacy of argatroban in the treatment of AIS. Three studies[6,11,12] ICH or major bleeding as an adverse reaction, which was not found in the fourth study[10].

**Main analysis**
We performed a meta-analysis of the four studies mentioned above. The efficacy of argatroban was controversial. Two studies reported superior improvements in the argatroban group than in the control group[6,11]. However, the other two studies did not find definitive effectiveness of argatroban in the treatment of AIS compared with the control groups[10,12]. The $P$ value of heterogeneity among the studies was significant ($P < 0.05$, $P = 74\%$), so the random-effects model was used for the analysis. The result showed that the overall effect was not significant (RR = 1.24; 95%CI: 0.74–2.10; $P = 0.42$) (Figure 2). Since there was considerable heterogeneity among the four studies, the result was not reliable. The nonconformity of enrollment criteria and result evaluation might have been the cause of the heterogeneity. We found that the inclusion and assessment criteria of two studies[6,12] performed in recent years were in good coincidence. Therefore, we only analyzed the results of these two studies. The results showed that the heterogeneity was insignificant ($P = 0.21$, $P = 36\%$). And the fixed-effects model was used for the analysis. The overall effect was also not significant (RR = 1.0; 95%CI: 0.72–1.39; $P = 0.99$) (Figure 3). The existing research results do not support the efficacy of argatroban in treating AIS.

In the three studies that assessed adverse reactions, none of them found that argatroban increased the risk of bleeding. Detailed data were not provided by Kobayashi et al[11], so only the studies of Barreto et al[6] and LaMonte et al[12] were
### Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Title</th>
<th>Country</th>
<th>Multiple/single center</th>
<th>Date</th>
<th>Argatroban/control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin inhibition in the acute phase of IS using argatroban</td>
<td>Japan</td>
<td>Single center</td>
<td>1995</td>
<td>7/6</td>
</tr>
<tr>
<td>Effect of the argatroban in acute cerebral thrombosis</td>
<td>Japan</td>
<td>Multicenter</td>
<td>1997</td>
<td>59/59</td>
</tr>
<tr>
<td>Argatroban in patients with acute ischemic stroke</td>
<td>United States</td>
<td>Multicenter</td>
<td>2004</td>
<td>86/47</td>
</tr>
<tr>
<td>Randomized, multicenter trial of ARTSS-2 (Argatroban with Recombinant Tissue Plasminogen Activator for Acute Stroke)</td>
<td>United States</td>
<td>Multicenter</td>
<td>2017</td>
<td>61/29</td>
</tr>
</tbody>
</table>

**Figure 1** Flow chart of article search and selection for this meta-analysis.

**Figure 2** Forest plot showing that there was no significant difference in efficacy among the studies. The results might not be reliable considering the heterogeneity.

Include in our analysis. The heterogeneity of the two studies was insignificant (\( P = 0.54, \ P = 0 \% \)) and the fixed-effects model was used. The overall analysis showed that there was no significant difference between the argatroban and control groups (RR = 1.34; 95% CI: 0.66–2.74; \( P = 0.42 \)) (Figure 4). The results indicated that argatroban does not increase the risk of bleeding in AIS. In all the four studies, there was no gender difference between the argatroban and control groups (\( P > 0.05 \)). The safety and efficacy of argatroban were not assessed according to gender. Therefore, the impact of gender on the safety and efficacy of argatroban cannot be evaluated. We analyzed the impact of patient age. In the studies of Barreto et al\(^6\), Kari et al\(^10\), and Kobayashi et al\(^11\), the mean age of different groups was described but comparisons were not made. In LaMonte et al\(^12\)'s study, there was an age difference between the arga-
Figure 3 Marian’s and Andrew’s studies were performed recently. The heterogeneity was within the acceptable limit. Although the results were different, the overall meta-analysis showed no difference.

Figure 4 Only Marian’s and Andrew’s studies provided detailed data of bleeding events. Analysis showed no difference compared with the control group.

troban and control groups ($P = 0.038$), but the results were not grouped by age. Therefore, the variable of age cannot be analyzed. In Barreto et al.[6]’s study, medical history was described, and patients may have had prior stroke, hypertension, coronary artery disease, diabetes mellitus, heart failure, or atrial fibrillation. However, the impact of comorbidity on the efficacy and safety of argatroban was not analyzed. None of the studies mentioned whether the patients had renal or liver disease. Therefore, the metabolism of argatroban cannot be evaluated.

**DISCUSSION**

Although the results of this meta-analysis suggested that argatroban did not increase the risk of ICH in the acute phase of cerebral infarction, it failed to show the advantage of argatroban over other drugs in the treatment of AIS. Anticoagulants have been used to treat AIS for > 70 years[13]. The use of anticoagulants for prevention and treatment of IS is still controversial. Anticoagulants are effective in preventing recurrence of cerebral infarction but can also cause bleeding. So far, there is no evidence to support short or long-term benefit of anticoagulants for patients with AIS[14], and more evidence-based data are needed.

Argatroban is a small-molecule thrombin inhibitor that was first synthesized by Japanese scientists[15]. It can inhibit coagulation by interacting with the catalytic site of thrombin reversibly[16]. Compared with other anticoagulant drugs, argatroban has some advantages. First, argatroban can penetrate and inhibit thrombin effectively despite the fibrin barrier, benefiting from its small molecular size. That means that argatroban has a therapeutic effect on more organized thrombi[5]. Second, argatroban acts quickly. Normally, it can reach steady-state plasma levels in 1–3 h after intravenous administration. Besides, the dose–response curve of argatroban is steady and predictable, which means that it has a wide margin of safety of dose titration[17, 18]. Third, argatroban is metabolized rapidly in the liver. The elimination half-life is 39–51 min and is mostly affected by hepatic function, despite age, gender, and renal function[19]. Although there is no specific antidote, the coagulation parameters generally return to normal within 2–4 h after withdrawal of argatroban, as long as liver function is normal[20]. Also, its pharmacological mechanism is selective and it hardly influences other serine proteases.
At present, argatroban is mainly used to treat heparin-induced thrombocytopenia [21]. In Japan and Korea, it has also been used to treat AIS[19]. Several reports have shown that argatroban is effective in treating AIS. Compared with high-dose aspirin (300 mg daily), argatroban plus standard-dose aspirin (100 mg daily) was as effective and safe for the treatment of moderate AIS[22]. Several single-center, nonrandomized, controlled studies have found that argatroban is effective for treating AIS[23-25].

However, the number of patients enrolled in the published studies was small and the studies were all carried out in Asia. In addition to the anticoagulant effect, some studies have shown that argatroban can improve ischemic symptoms by ameliorating cerebral blood flow in patients with AIS[26,27]. However, the number of studies is small and evidence-based medicine is insufficient. Therefore, these findings cannot be extrapolated to clinical application.

The efficiency and safety of argatroban in treating cardiogenic and non-cardioembolic stroke have differed among studies. A retrospective study in Japan analyzed the efficacy and safety of argatroban in the treatment of cardiogenic stroke. The study divided 2529 eligible patients into heparin, argatroban, and control (not receiving anticoagulant or antiplatelet therapy) groups, and the results showed that both heparin and argatroban decreased the risk of death from stroke, but the risk of bleeding was not increased in the argatroban group[28]. However, for non-cardioembolic stroke, the efficiency of argatroban was indefinite. A study including 2289 pairs of patients with atherothrombotic stroke was performed in 2016. The results showed that, despite its safety, argatroban yielded no additional benefit for acute atherothrombotic stroke[29]. Another study found that argatroban was not superior to control therapy in non-cardioembolic AIS[30]. On the contrary, a recent retrospective study of 1325 patients found that argatroban was safe and effective for improving short and long-term outcomes in patients with non-cardioembolic AIS[31]. The results of the studies above indicate that argatroban might have a better therapeutic effect in treating cardiogenic stroke than non-cardioembolic stroke. In Japan, argatroban has already been recommended for patients without embolic IS within 48 h of onset in their 2013 guidelines for management of IS[32]. However, for acute non-cardioembolic stroke, the benefit of argatroban is not definite, and the drug has not been recommended in any treatment guidelines. Most of the recent studies were performed in Japan and were retrospective. More high-quality studies from other regions are needed to support the advantages of argatroban in treating cardiogenic stroke.

As far as we know, this study is the first systematic review of the safety and efficacy of argatroban for treatment of AIS. We only analyzed four studies. We found considerable heterogeneity among the studies. Clinical heterogeneity might occur for many reasons, such as geographic region, racial difference in severity of initial symptoms, and interference with other treatment. The four studies were not designed to the same standard, which may have caused heterogeneity. Also, subgroup analysis was not possible because of the absence of detailed data. Although we did not find evidence supporting the efficacy of argatroban for treatment of AIS, there were some shortcomings in our study. First, we found considerable heterogeneity in the data sources. We only analyzed four studies. The small sample size limits the credibility of the results and was the main source of the heterogeneity. The chronological span of the four studies was large. Kario et al.'s and Kobayashi et al.'s studies were performed in 1995 and 1997, respectively. The inclusion criteria were not fully described in these studies. Both reported clinical improvement, but the assessment tools and criteria for evaluation were not listed clearly. On the contrary, the studies of Barreto et al.[6] and LaMonte et al.[12] had unified standards. The heterogeneity of all four studies was large, but was smaller in the studies of Barreto et al.[6] and LaMonte et al.[12]. Differences in inclusion and assessment criteria may have caused heterogeneity. Besides, the clinical characteristics of patients enrolled in the studies of Kario et al.[10] and Kobayashi et al.[11] were not described in detail. Thus, it was hard to perform subgroup analysis and meta-regression. We are not able to analyze the specific reason for the heterogeneity, and the heterogeneity made it hard to draw a significant conclusion. However, the quality of the other two recent studies was higher. The inclusion and assessment standards were unified and the heterogeneity of the studies was small. Although the two studies yielded different results on efficacy, the meta-analysis still found no evidence supporting the therapeutic effect of argatroban in AIS. However, the conclusion is debatable due to the limited amount of research and its quality. We might conclude that it is safe to use argatroban for treatment of AIS, but the efficacy needs verification. More high-quality surveys with a large sample are needed in the future for more reliable results. Therefore, our results need to be interpreted with caution.
CONCLUSION

Patients with AIS might not benefit from argatroban and combination therapy with argatroban does not increase bleeding tendency.

ARTICLE HIGHLIGHTS

Research background
Acute ischemic stroke (AIS) has been a global health challenge. And new treatments have been explored. Argatroban as a novel direct thrombin inhibitor has been used in treating AIS. However, the exact efficiency and safety remain unclear.

Research motivation
The drug safety of argatroban has been proved by many studies. However, the results of present studies on evaluating curative effect of argatroban on AIS were quite controversial, which has puzzled us in confirming the role of argatroban in AIS treatment. Therefore, it is necessary to do such an analysis to further evaluate the efficiency and safety of argatroban in treating AIS.

Research objectives
The objective of this study was to evaluate the efficiency and safety of argatroban in treating AIS by extracting available data from existing studies.

Research methods
We have searched database PubMed, Embase, Science, Medline, and Cochrane Library to retrieve all of the studies associated with argatroban and AIS. Only randomized controlled clinical studies were screened for this review. Meta-analysis methodology was used and the standard mean difference values and 95% confidence intervals were estimated to get final results.

Research results
Only four studies that met the criteria were included in our review, which contained a total of 354 cases with 213 cases in the argatroban group and 141 in the control group. The overall analysis showed that patients with AIS did not improve more with argatroban treatment. And argatroban did not increase the bleeding risk in AIS patients.

Research conclusions
Our study that integrated the existing data suggested that patients with AIS might not benefit more from argatroban and combination therapy with argatroban will not increase bleeding tendency.

Research perspectives
More high-quality studies are needed for further evaluation of the efficacy and safety of argatroban in treating AIS.

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Efficacy and safety evaluation of argatroban


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Biologic therapy for Crohn’s disease over the last 3 decades

Ji-Liang Shen, Zheng Zhou, Jia-Sheng Cao, Bin Zhang, Jia-Hao Hu, Jia-Ying Li, Xiao-Ming Liu, Sarun Juengpanich, Ming-Song Li, Xu Feng

ORCID number: Ji-Liang Shen 0000-0001-9702-4735; Zheng Zhou 0000-0002-0390-9135; Jia-Sheng Cao 0000-0002-4047-8899; Bin Zhang 0000-0002-6888-811X; Jia-Hao Hu 0000-0001-5835-1012; Jia-Ying Li 0000-0001-7508-1579; Xiao-Ming Liu 0000-0003-3990-419X; Sarun Juengpanich 0000-0002-1449-5564; Ming-Song Li 0000-0003-2115-5928; Xu Feng 0000-0002-4445-8174.

Author contributions: Shen JL and Feng X designed the study and collected the data; Shen JL, Zhou Z, and Cao JS analyzed and interpreted the data; Zhou Z, Cao JS, Zhang B, Hu JH, Li JY, Liu XM, and Li MS wrote the manuscript; Juengpanich S and Feng X revised the manuscript; all authors made final approval of the version of the manuscript.

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Abstract

BACKGROUND

Despite the overload of publications on Crohn’s disease (CD), no comprehensive analysis of biologic therapy for CD has been reported.

AIM

To determine knowledge gaps and identify areas of interest of biologic therapy for CD.

METHODS

The top 100 highest-cited original articles were identified from January 1991 to December 2020 in the Clarivate Analytics Web of Science Core Collection database. We conducted a bibliometric analysis of biologic therapy for CD based on total citations, summarized the bibliographic information of the articles related to CD biologic therapy, and explored the research hotspots.

RESULTS

The top 100 highest-cited original articles were identified with total citations ranging from 307 to 2978. The 2000s (Period II, n = 66) yielded the most influential original articles and saw the most dramatic growth. Among the top 10 countries, including 8 European countries and 2 North American countries, the United States (n = 37) and Belgium (n = 20) contributed the most publications. Among the top 10 institutions, the University Hospital Gasthuisberg in Belgium (n = 23), the University of Chicago in the United States (n = 20), and the Mayo Clinic in the United States (n = 17) published the most papers. Regarding authors, Rutgeerts P in Belgium (n = 32), Sandborn WJ in the United States (n = 23), and Feagan BG in
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DOI: https://dx.doi.org/10.12998/wjcc.v10.i2.594

INTRODUCTION

Crohn’s disease (CD), the main type of inflammatory bowel disease, is characterized as chronic, refractory, and relapsing transmural inflammation of the digestive tract[1]. Due to the continuous activation of the intestinal immune system, CD patients would suffer chronic abdominal pain, diarrhea, weight loss, malnutrition, and other obstructive symptoms[2]. Previously, the therapeutic strategy for CD was limited to corticosteroids[3], immunomodulators [methotrexate and thiopurines (azathioprine and mercaptopurine)][4-6], and surgery[7,8]. In the past 3 decades, multiple biologics emerged for CD management, including anti-tumor necrosis factor (TNF) agents (infliximab, adalimumab, and certolizumab), anti-integrin agents (vedolizumab and natalizumab), and anti-(IL)-12/23 agent (ustekinumab)[9]. However, it is difficult for researchers to gain critical articles to guide their studies owing to the publication overload of varied scientific quality.

Bibliometrics is an increasingly conducted method for analyzing and summarizing the main characteristics of publications, including the citation count, the cooperative relationships among countries, institutions, and authors, the distribution of journals, and the hotspots in a certain field. By performing bibliometric analysis and creating infographics, researchers can identify and capture the research hotspots and rising patterns. Bibliometric analysis has been broadly performed in various diseases of gastroenterology, such as Helicobacter pylori infection[10], irritable bowel syndrome [11], acute pancreatitis[12], inflammatory bowel disease[13], and so on. Although Connelly et al[14] conducted a bibliometric analysis of the 100 classic articles in ulcerative colitis and offered a reference of highly-citable manuscripts, no bibliometric analysis of biologic therapy for CD has been reported.

In this study, we aimed to analyze the top 100 highest-cited original articles in the field of biologic therapy for CD over the last 3 decades via bibliometric citation analysis.
analysis based on the total citations (TC), which reflect the direct academic significance of a study. In turn, the analysis would provide clinicians and researchers the meaningful insights into the future directions related to biologic therapy for CD.

MATERIALS AND METHODS

Literature search and screening
A systematic search of literature from January 1991 to December 2020 was performed in the Clarivate Analytics Web of Science Core Collection (WOSCC) database. We used search terms including “biologic therapy,” “Crohn disease,” “anti-tumor necrosis factor,” “infliximab,” “adalimumab,” “certolizumab,” “anti-integrin,” “vedolizumab,” “natalizumab,” “anti-IL-12/23,” “ustekinumab,” and their synonyms. The search strategy was shown in Supplementary Table 1. Original articles whose main topic was biologic therapy for CD were included. Literature that was not related to biologic therapy for CD was excluded, and reviews, commentary, case reports, editorials, consensus statements, and guidelines were also excluded. Two reviewers (J.L.S. and Z.Z.) independently identified the top 100 highest-cited original articles based on TC, and a third reviewer (J.S.C.) was recruited for discussion until any disagreement was settled.

Statistical analysis
After identifying the top 100 highest-cited original articles, the records with all available information were downloaded from the WOSCC database. Then, the bibliographic information of the top 100 highest-cited studies was converted and analyzed automatically by R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) with the “bibliometric” package[15]. We further extracted and analyzed the information, including title, author, institution, country, TC, publication year, journal, 2020 Journal Citation Reports impact factor (IF), and keywords, using the “bibliometric” package.

All collected data were entered in a spreadsheet and manipulated using Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, United States). Graphs and figures were created by using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Microsoft Excel 2019 Power Map (Microsoft Corp., Redmond, WA, United States) was utilized for a global map of countries’ publications of the top 100 highest-cited original articles. We used the VOS viewer (Version 1.6.10) to produce author cooperation network map, institution cooperation network map, keyword clustering map, and so on. The cooperation network map among all countries and the tree map of keywords were created on an online platform of bibliometric analysis (https://bibliometric.com/). Finally, 2 researchers (Z.Z. and J.S.C) verified the collected data and further analysis independently.

RESULTS

Publication and citation count
A total of 5489 original articles focusing on biologic therapy for CD were identified from the WOSCC database from January 1991 to December 2020. The top 100 highest-cited original articles were listed in Supplementary Table 2 according to the descending order of TC, and the TC ranged from 2978[16] to 307[17]. The earliest influential original article, which focused on treating CD with anti-TNF and gained TC of 926, was published in 1995[18]. The latest original articles were 4 studies published in 2017 that focused on biologic therapy for CD, including infliximab, adalimumab, and vedolizumab. Both the annual and the cumulative number of publications over the last 3 decades were presented in Figure 1. Interestingly, the 2000s (Period II, n = 66) yielded the most influential original articles and saw the most dramatic growth of them, followed by the 2010s (Period III, n = 28) and the 1990s (Period I, n = 6). Notably, the annual number of publications reached a peak of 11 in the year 2007 in Period II.

Countries
In analyzing the countries to identify the high-impact countries in this field, the top 100 highest-cited original articles originated from 15 countries (Figure 2). The top 10 countries with the most publications were listed in Table 1, including 8 European countries and 2 North American countries. Among the top 100 highest-cited original
Table 1 Top 10 countries with the most publications

<table>
<thead>
<tr>
<th>Country</th>
<th>Publication</th>
<th>TC</th>
<th>TC/Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
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<tr>
<td>Belgium</td>
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</tr>
<tr>
<td>France</td>
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</tr>
<tr>
<td>United Kingdom</td>
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<td>Switzerland</td>
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</tr>
</tbody>
</table>

TC: Total citation.

The United States published the most articles (n = 37), followed by Belgium (n = 20), France (n = 9), Germany (n = 9), Spain (n = 6), United Kingdom (n = 5), Netherlands (n = 4), Norway (n = 2), Canada (n = 2), and Switzerland (n = 1). Notably, the United States has contributed the most studies and TC in the field of biologic therapy for CD, publishing 37 influential articles and 26179 citations. Meanwhile, as the top high-yield country in Europe, Belgium has published 20 articles with a TC of 13325. The ratio of TC to publication represented the average number of citations of each article, namely the average influence of each study. Although Switzerland ranked tenth in the number of original articles, contributing merely 1 article, it had the highest TC/Publication of 872. To be specific, Hueber W et al.[19] from Switzerland conducted a randomized, double-blind placebo-controlled trial to explore the effect of a human anti-IL-17A monoclonal antibody, namely secukinumab, for moderate to severe CD, and they failed that blockade of IL-17A was ineffective and caused higher rates of adverse events. Thus, the scientific quality of the research in Switzerland may be generally high. Figure 3 showed the cooperation relationships among countries that contributed to the top 100 highest-cited original articles. The United States, Belgium,
France, and Germany were intuitively observed to be involved in the close partnership.

**Institutions**

The top 10 institutions with the most publications were listed in Table 2, including the University Hospital Gasthuisberg in Belgium, the University of Chicago in the United States, and the Mayo Clinic in the United States with 23, 20, and 17 papers, respectively, and with 17529 citations, 19342 citations, and 14879 citations, respectively. Although the University of Chicago ranked second in the publications, it had the highest TC/Publication of 967, followed by the University of Western Ontario (TC/Publication = 952), the University of Pennsylvania (TC/Publication = 909), and the University Hospital Kiel (TC/Publication = 907). The average citations per article exceeded 900 for these 4 institutions above. The cooperation between institutions was a critical factor in promoting technological development, and Figure 4 showed the cooperation relationships of institutions that have co-published more than three top-
Table 2 Top 10 institutions with the most publications

<table>
<thead>
<tr>
<th>Institutions</th>
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<tr>
<td>Abbott Labs</td>
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<td>4614</td>
<td>769</td>
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</table>

TC: Total citation.

Table 3, including Rutgeerts P in Belgium, Sandborn WJ in the United States, and Feagan BG in

Authors

The top 10 most influential authors with the most publications were listed in Table 3, including Rutgeerts P in Belgium, Sandborn WJ in the United States, and Feagan BG in
### Table 3 Top 10 authors with the most publications

<table>
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<tr>
<td>Panaccione R</td>
<td>9</td>
<td>5976</td>
<td>664</td>
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</tbody>
</table>

TC: Total citation.

---

**Figure 4** Cooperation relationships of institutions that have co-published more than three top-cited articles.

Canada with 32, 23, and 18 papers, respectively, and with 26039 citations, 18034 citations, and 16127 citations, respectively. Notably, Hanauer SB in the United States had the highest TC/Publication with merely 14 publications, which meant that his studies were of high scientific quality. The partnership among authors that have co-published more than 3 top-cited articles was shown in **Figure 5**.

### Journals

Based on the descending order of the number of the top 100 most influential original articles, the top 10 journals were listed in **Table 4**. Over the last 3 decades, *Gastroenterology* (IF = 22.682) has published the extremely most articles on biologic therapy for CD, including 32 publications and 17654 TC. Among the top 10 most influential journals, 5 journals had TC/Publication exceeding 500, in which *The New England Journal of Medicine* had the highest IF of 91.245, the highest TC of 18379, and the highest TC/Publication of 1225, exceeding 90, 18000, and 1225, respectively. The rest were *The Lancet* (IF = 79.321, TC/Publication = 855), *Journal of Crohn’s and Colitis* (IF = 9.071, TC/Publication = 799), *Annals of Internal Medicine* (IF = 25.391, TC/Publication = 668), and *Gastroenterology* (IF = 22.682, TC/Publication = 552).
Table 4 Top 10 journals with the most publications

<table>
<thead>
<tr>
<th>Journal</th>
<th>Publication</th>
<th>2020 IF</th>
<th>TC</th>
<th>TC/Publication</th>
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<td>32</td>
<td>22.682</td>
<td>17654</td>
<td>552</td>
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<td>New England Journal of Medicine</td>
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<td>91.245</td>
<td>18379</td>
<td>1225</td>
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<td>Gut</td>
<td>10</td>
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<td>855</td>
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<td>25.391</td>
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</table>

TC: Total citation; IF: Impact factor.

Analysis of keywords

The research hotspots in the field of biologic therapy for CD were explored and demonstrated in the treemap (Figure 6). Infliximab, tumor necrosis factor, monoclonal antibody, and adalimumab accounted for 9%, 5%, 3%, and 2% of keywords, respectively. The cluster analysis of keywords that appeared more than seven times was also conducted to validate the results (Figure 7).

DISCUSSION

Due to the lack of a systematic approach to identifying the important information, it is challenging for clinicians and researchers to review the development of biological therapy for CD over the past 3 decades. In the study, we identified and ranked the top 100 highest-cited original articles by TC according to the WOSCC database. Through the bibliometric analysis, we summarized the basic characteristics of these original articles, such as publication, citation, countries, institutions, authors, journals, and keywords. In addition, we could identify research hotspots of biologic therapy for CD.
The analysis of annual and cumulative publications in different publication periods (Period I, Period II, and Period III) enabled clinicians and researchers to understand the development of biologic therapy for CD intuitively. In the 1990s (Period I), the number of most influential articles grew slowly. Notably, there was an explosive growth of the number of studies in the 2000s (Period II) because the first biologic agent, infliximab, was approved for CD treatment by the Food and Drug Administration[20]. Meanwhile, an increasing number of clinical trials were designed and conducted during Period II, including the ACCENT I trial (maintenance infliximab for CD)[16], the CLASSIC I and II trials (maintenance adalimumab for CD)[21,22], the CHARM trial (maintenance adalimumab for clinical response and remission of CD)
CONCLUSION

In summary, the top 100 highest-cited original articles of biologic therapy for CD over the last 3 decades were identified and entered a bibliometric analysis to provide useful insights for clinicians and researchers. Moreover, the study offered an overview of countries, institutions, authors, and journals that had contributed significantly to the study of biologic therapy for CD, thus generating the most high-cited original articles with the highest TC in this field. Rutgeerts P from Belgium and Sandborn WJ from the United States have published the most influential studies and made excellent contributions to biologic therapy for CD, which was worth remembering. More attention should be paid to international cooperation, but it is not limited to the United States and Europe. Further multicenter clinical trials among different countries should be performed to offer evidence for biologic therapy for CD in the future.

Various medical journals were engaged in promoting the development of biologic therapy for CD. In terms of influence, the top 10 journals with the most publications were Gastroenterology, The New England Journal of Medicine, and Gut, with a total of 57 articles. The others were The Lancet, Clinical Gastroenterology and Hepatology, American Journal of Gastroenterology, Journal of Crohn’s and Colitis, Inflammatory Bowel Disease, Arthritis Rheumatology, and Annals of Internal Medicine, making a total of 27 publications. The top 10 journals were mostly in the field of digestive diseases, while some of them were comprehensive journals, namely The New England Journal of Medicine and The Lancet. Both journals have relatively high IF of 91.245 and 79.321, respectively, with high TC/Publication of 1225 and 855, respectively. The high scientific level of clinical trials in the top-cited original articles could contribute a lot to the higher citations per paper. One of the significant clinical trials, which was called the ACCENT I randomized trial, was focused on maintenance infliximab for CD and published in The Lancet with the highest TC of 2978[16].

The research hotspots in the top 100 highest-cited original articles over the past 3 decades were infliximab, tumor necrosis factor, monoclonal antibody, and adalimumab treatment for CD, which belonged to the anti-TNF research. The anti-TNF biologics were approved by Food and Drug Administration in an early stage and have achieved excellent curative effects in clinical use. However, other biologics such as anti-integrin agents (vedolizumab and natalizumab) and anti-IL-12/23 agents (ustekinumab) emerged later, and most of them were still in the clinical trial stage. Thus the related original articles have not gained high TC. However, more influential articles would be published as the studies of novel biologics continue.

The study had several limitations that needed to be discussed. First, the current study may not include all influential articles in the field of biologic therapy for CD merely based on the WOSCC database. Although we did utilize broad search terms to search all related articles, it is possible that the search strategy may have missed some crucial literature. Further bibliometric analysis would be conducted with a precise search strategy from WOSCC, PubMed, and PMC databases. Second, the potential citation biases may affect the list of the top 100 highest-cited original articles and subsequently generate inaccurate results. In particular, the latest articles may have insufficient time to accumulate TC. Inappropriate citations, including self-citations, institutional biases, powerful author biases, and language biases, may also be inevitable and further affect the results of the analysis potentially.
development of the specialized field. We focused on study keywords to explore the current and future research hotspots of biologic therapy for CD. Undoubtedly, studies and innovation of the field will continue to evolve and become an area of interest in the future.

**ARTICLE HIGHLIGHTS**

**Research background**
There is an overloading amount of publications on biologic therapy for Crohn’s disease (CD).

**Research motivation**
No comprehensive analysis of biologic therapy for CD has been reported.

**Research objectives**
To determine knowledge gaps and identify areas of interest of biologic therapy for CD.

**Research methods**
We conducted a bibliometric analysis of biologic therapy for CD based on the top 100 highest-cited original articles, summarized the bibliographic information, and explored the research hotspots.

**Research results**
The 2000s yielded the most influential original articles and saw the most dramatic growth. The United States and Europe contributed the most publications, and the cooperation relationships between them were most frequent. *Gastroenterology* published the most articles on biologic therapy for CD. Anti-tumor necrosis factor biologics and monoclonal antibodies were the most studied topics.

**Research conclusions**
The bibliometric analysis emphasized the key contributions made to the development of the specialized field.

**Research perspectives**
These data would provide useful research insights into biologic therapy for CD for clinicians and researchers.

**ACKNOWLEDGEMENTS**
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25  Kane SV, Horst S, Sandborn WJ, Becker B, Neis B, Moscandrew M, Hanson KA, Tremaine WJ,


Novel compound heterozygous GPR56 gene mutation in a twin with lissencephaly: A case report

Wen-Xin Lin, Ying-Ying Chai, Ting-Ting Huang, Xia Zhang, Guo Zheng, Gang Zhang, Fang Peng, Yan-Jun Huang

Abstract

BACKGROUND
Lissencephaly (LIS) is a malformation of cortical development with broad gyri, shallow sulci and thickened cortex characterized by developmental delays and seizures. Currently, 20 genes have been implicated in LIS. However, GPR56-related LIS has never been reported. GPR56 is considered one of the causative genes for bilateral frontoparietal polymicrogyria. Here, we report a twin infant with LIS and review the relevant literature. The twins both carried the novel compound heterozygous GPR56 mutations.

CASE SUMMARY
A 5-mo-old female infant was hospitalized due to repeated convulsions for 1 d. The patient had a flat head deformity that manifested as developmental delays and a sudden onset of generalized tonic-clonic seizures at 5 mo without any causes. The electroencephalography was normal. Brain magnetic resonance imaging revealed a simple brain structure with widened and thickened gyri and shallow sulci. The white matter of the brain was significantly reduced. Patchy long T1 and T2 signals could be seen around the ventricles, which were expanded, and the extracerebral space was widened. Genetic testing confirmed that the patient carried the GPR56 gene compound heterozygous mutations c.228delC (p.F76fs) and c.1820_1821delAT (p.H607fs). The unaffected father carried a heterozygous c.1820_1821delAT mutation, and the unaffected mother carried a heterozygous c.228delC mutation. The twin sister carried the same mutations as the proband. The patient was diagnosed with LIS.

CONCLUSION
This is the first case report of LIS that is likely caused by mutations of the GPR56 gene.

**Key Words:** Lissencephaly; Epilepsy; GPR56 mutations; Compound heterozygous mutations; Case report

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**Core Tip:** We report a twin infant with lissencephaly (LIS). The twins both carried the novel compound heterozygous *GPR56* mutations, p.F76fs and p.H607fs, which have not been reported in the Human Gene Mutation Database. To our knowledge, this is the first case of *GRP56*-related LIS. Therefore, *GPR56* gene mutations may lead to LIS.

**INTRODUCTION**

Lissencephaly (LIS) is a group of abnormal cerebral cortical dysplasias caused by the defective migration of neurons. It can be diagnosed clinically by neuroimaging. It is characterized by thickening of the cerebral cortex, widening of the gyri, and disappearance or shallowness of the sulci. The complete disappearance of the sulci and gyri showing smooth surface of the brain is called agyria and is seen in severe cases [1]. According to the neuroimaging, LIS is divided into six grades, ranging from severe agyria (grade 1) to mild subcortical band heterotopias (grade 6). The severity of nerve damage is closely related to the grade of LIS and cortical thickening, and the mortality rate of severe LIS is high[2]. In the early stages, patients often exhibit developmental delays and hypotonia, followed by seizures, and a severe intellectual disability eventually. Although a LIS patient may develop normally in the neonatal period, many neonates suffer from persistent feeding problems and different types of epilepsy, which are difficult to cure[3]. An individual with mild LIS and normal intelligence has been reported[4]. Currently, 20 genes have been implicated in LIS. Many of these genes are microtubule genes[5,6].

*GPR56* (OMIM#606854, NM_0001145773) encodes an orphan G protein-coupled receptor (GPCR) that is extensively expressed in the nervous system and is essential for the normal development of the cerebral cortex and cerebellar morphology[7-9]. The reported mutations of the *GPR56* gene have been confirmed to be related to bilateral frontoparietal polymicrogyria (BFPP)[10].

Herein, we report a twin infant with LIS who came from a nonconsanguineous family. The twins both carried a novel compound heterozygous *GPR56* mutation. To our knowledge, this is the first case of *GRP56*-related LIS.

**CASE PRESENTATION**

**Chief complaints**

A 5-mo-old female infant was hospitalized due to repeated convulsions for 1 d.

**History of present illness**

The patient was admitted to the Children’s Hospital of Nanjing Medical University due to repeated convulsions. The patient had a sudden onset of generalized tonic-clonic seizures without any causes. In addition, she had a flat head deformity and developmental delays.
**History of past illness**
The patient had no history of past illness.

**Personal and family history**
The patient was the first child of nonconsanguineous Chinese parents. She was delivered by cesarean section due to twin pregnancy at 32 wk of gestation, with a birth weight of 2.6 kg. No intrauterine distress or postnatal asphyxia had occurred. She had a twin sister with LIS.

**Physical examination**
The patient showed a flat head deformity. The neurological examination was normal. There were no other abnormal signs.

**Laboratory examinations**
The electroencephalography and laboratory findings (full blood count, liver, kidney and thyroid function tests, creatine kinase, uric acid, metabolic study and chromosome karyotyping) were normal.

**Imaging examinations**
Brain magnetic resonance imaging (MRI) revealed a simple brain structure, with widened and thickened gyri and shallow sulci. The white matter of the brain was significantly reduced. The patchy long T1 and long T2 signals could be seen around the ventricles, which were expanded, and the extracerebral space was widened (Figure 1).

**FINAL DIAGNOSIS**
According to the clinical characteristics, imaging and genetic test findings (Figure 2), the infant was diagnosed with LIS.

**TREATMENT**
During the hospital stay, the patient had no epileptic seizures. She received rehabilitation, but anti-epileptic treatment was refused.

**OUTCOME AND FOLLOW-UP**
The patient experienced repeated convulsions after she was discharged from hospital. The convulsions occurred once a day to more than ten times a day without any causes, each episode lasting several minutes. She died 3 mo later.

**DISCUSSION**
The GPR56 gene spans 45 kb and consists of 14 exons encoding an orphan GPCR of 693 amino acids[7,11]. GPR56 is a member of the adhesion GPCR family, which has an N- and a C-terminal fragment and a GPCR proteolytic site[12]. In the central nervous system, GPR56 plays an important role in the normal development of the cerebral cortex and cerebellar morphogenesis[8]. In the peripheral nervous system, GPR56 can regulate the formation and maintenance of myelin sheaths[13]. Therefore, the normal expression of GPR56 is essential for the function of the nervous system.

It is known that mutations of the GPR56 gene are related to BFPP (Table 1). The clinical manifestations of BFPP are overall growth retardation and seizures. MRI shows symmetrical polygyria (the frontal parietal area is the most serious part), ventricular enlargement, and bilateral white matter changes. Twenty-eight pathogenic GPR56 mutations related to the BFPP phenotype have been reported[11,14]. The affected individuals inherit the mutants in an autosomal recessive mode. The majority of missense mutations resulted in similar clinical symptoms, indicating that the similar phenotype might be caused by the same mechanism. However, the mechanism remains unclear, although it may involve GPR56 trafficking and a decrease in receptor
<table>
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<th>Ethnicity</th>
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<th>Seizure</th>
<th>MRI</th>
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<th>White matter abnormalities</th>
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<td>First cousin</td>
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<td>+</td>
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<td>Israeli Jewish</td>
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<td>Severe</td>
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<td>+</td>
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<td>+</td>
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<td>GTC, myoclonic</td>
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**Parrini et al.** [18], 2009

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<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>Atypical absences, GTC, tonic</td>
<td>BFPP</td>
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<tr>
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<td>C</td>
<td>Severe</td>
<td>Infantile spasms, tonic and atonic seizures</td>
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**Bahi-Buisson et al.** [19], 2010

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<th>Family Relationship</th>
<th>Age</th>
<th>Seizure Type</th>
<th>BFPP</th>
<th>Signal Change</th>
<th>Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.174-175insC (p.E59fs*24)</td>
<td>Exon 3</td>
<td>2</td>
<td>NA</td>
<td>C</td>
<td>NA</td>
<td>Severe</td>
<td>NA</td>
<td>Patchy periventricular predominance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>Focal seizures</td>
<td>BFPP</td>
</tr>
<tr>
<td>c.272G&gt;A (p.C91Y)</td>
<td>Exon 3</td>
<td>2</td>
<td>NA</td>
<td>C</td>
<td>Walking at 2 yr</td>
<td>Severe</td>
<td>NA</td>
<td>Patchy periventricular and frontal predominance</td>
</tr>
<tr>
<td>c.367C&gt;T (p.Q123X)</td>
<td>Exon 3</td>
<td>1</td>
<td>NA</td>
<td>C</td>
<td>Walking at 2 yr</td>
<td>Severe</td>
<td>GTC, atypical absence, atonic seizures</td>
<td>BFPP</td>
</tr>
<tr>
<td>c.671delA (p.D224Wfs*96)</td>
<td>Exon 5</td>
<td>3</td>
<td>NA</td>
<td>C</td>
<td>Walking at 4 yr</td>
<td>Severe</td>
<td>GTC</td>
<td>BFPP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Walking at 18 mo</td>
<td>Severe</td>
<td>GTC</td>
<td>BFPP</td>
</tr>
<tr>
<td>c.1215-1216delC (p.L406S406fs*41)</td>
<td>Exon 10</td>
<td>1</td>
<td>NA</td>
<td>C</td>
<td>Sitting without support</td>
<td>Severe</td>
<td>GTC</td>
<td>BFPP</td>
</tr>
<tr>
<td>---</td>
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<tr>
<td>c.1254C&gt;G (p.C418W)</td>
<td>Exon 10</td>
<td>3</td>
<td>Pakistani</td>
<td>First cousin</td>
<td>Walking at 5 yr</td>
<td>Severe</td>
<td>GTC</td>
<td>BFPP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Walking at 5 yr</td>
<td>Severe</td>
<td>GTC</td>
<td>BFPP</td>
</tr>
<tr>
<td>c.1345delCTG (p.L449del)</td>
<td>Exon 11</td>
<td>1</td>
<td>NA</td>
<td>C</td>
<td>Walking at 3 yr</td>
<td>Severe</td>
<td>Atypical absence</td>
<td>BFPP</td>
</tr>
<tr>
<td>c.1453C&gt;T (p.S485P)</td>
<td>Exon 11</td>
<td>2</td>
<td>NA</td>
<td>C</td>
<td>Walking at 18 mo</td>
<td>Severe</td>
<td>Focal seizures, generalized tonic seizures</td>
<td>BFPP</td>
</tr>
<tr>
<td>Luo et al [20], 2011</td>
<td>c.1486G&gt;A (p.E496K)</td>
<td>NA</td>
<td>1</td>
<td>Yemeni</td>
<td>First cousin</td>
<td>Walking</td>
<td>Severe</td>
<td>Tonic-clonic seizures</td>
</tr>
<tr>
<td>Quattrocchi et al [16], 2013</td>
<td>c.105C&gt;A (p.C35X)</td>
<td>Exon 2</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>Ataxic gait</td>
<td>Severe</td>
<td>Focal seizures, myoclonic</td>
</tr>
<tr>
<td></td>
<td>c.429G&gt;A (p.W143X)</td>
<td>Exon 2</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>Ataxic gait</td>
<td>Moderate</td>
<td>No</td>
</tr>
<tr>
<td>Luo et al [20], 2011</td>
<td>c.1453C&gt;T (p.S485P)</td>
<td>Exon 11</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>Walking at 18 mo</td>
<td>Severe</td>
<td>GTS, focal seizures</td>
</tr>
<tr>
<td>Reference</td>
<td>Mutation</td>
<td>Exon(s)</td>
<td>Consanguineous</td>
<td>Language</td>
<td>Age of Onset</td>
<td>Seizures</td>
<td>BFPP</td>
<td>MRI</td>
</tr>
<tr>
<td>-----------</td>
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<td>-----</td>
</tr>
<tr>
<td>Fujii et al. [21], 2014</td>
<td>c.107G&gt;A and c.113G&gt;A (p.S36N and p.R38Q)</td>
<td>Exon 2</td>
<td>Japanese</td>
<td>Korean</td>
<td>1</td>
<td>Able to walk with help</td>
<td>Severe</td>
<td>Complex partial seizures, tonic seizures, epileptic spasms</td>
</tr>
<tr>
<td>Desai et al. [22], 2015</td>
<td>c.113G&gt;A (p.R38Q)</td>
<td>Exon 3</td>
<td>Indian</td>
<td>(Marathi)</td>
<td>1</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Complex febrile seizures</td>
</tr>
<tr>
<td></td>
<td>c.739-746 delCAGGACC (p.Q246Tfx*72)</td>
<td>Exon 4</td>
<td>Indian</td>
<td>(Punjabi)</td>
<td>1</td>
<td>Severe</td>
<td>Mild</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>c.1426 C&gt;T (p.R476X)</td>
<td>Exon 12</td>
<td>Indian</td>
<td>(Gujarati)</td>
<td>1</td>
<td>Severe</td>
<td>Severe</td>
<td>Generalized seizures</td>
</tr>
<tr>
<td></td>
<td>811C &gt; T (R271X)</td>
<td>Exon 6</td>
<td>Caucasian</td>
<td>1</td>
<td>Severe</td>
<td>Severe</td>
<td>Hot water epilepsy</td>
<td>BFPP</td>
</tr>
<tr>
<td>Öncü-Öner et al. [14], 2018</td>
<td>811C &gt; T (R271X)</td>
<td>Exon 6</td>
<td>NA</td>
<td>C</td>
<td>Severe</td>
<td>Severe</td>
<td>Focal onset bilateral tonic-clonic seizure</td>
<td>BFPP</td>
</tr>
<tr>
<td>Current report</td>
<td>c.228delC and c.1820-1821del AT (p.F76fs and p.H607fs)</td>
<td>Exon 6 and Exon 13</td>
<td>Chinese</td>
<td></td>
<td>2</td>
<td>*</td>
<td>Severe</td>
<td>GTC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AS: Absence of seizure; BFPP: Bilateral frontoparietal polymicrogyria; C: Consanguineous; FS: Febrile seizure; GTC: General tonic-clonic seizures; LIS: Lissencephaly; MRI: Magnetic resonance imaging; N: Nonconsanguineous; NA: Not available; UAE: United Arab Emirates.

GPR56 knockdown did not affect the migration of neural progenitor cells, while GPR56 overexpression inhibited the migration of neural progenitor cells. This mechanism might occur through the reorganization of cerebral cortex actin to change the cell morphology and regulate neural progenitor cell behavior [8]. LIS is caused by premature stop of neuronal migration, which might explain the mechanism of the GPR56 mutations causing LIS in the present case.
Lin WX et al. GPR56 mutation in a twin infant with lissencephaly

Figure 1 Brain magnetic resonance imaging of the proband revealed a simple brain structure, with widened and thickened gyri and shallow sulci.

The development of the brain is a delicate and complex physiological process, and the proper migration of neurons is one of the most critical steps. LIS is brain dysplasia caused by the premature stop of neuronal migration. Type I LIS is characterized by a thickened cerebral cortex (10-20 mm, whereas normal is 4 mm), but no other brain development malformations, such as severe congenital microcephaly, corpus callosum hypoplasia, or cerebellar hypoplasia[2]. Microscopically, the cerebral cortex in LIS is divided into four thick and dysplastic layers: The molecular layer, the superficial cellular layer, the cell spare layer, and the deeper cellular layer; the normal cerebral cortex has six layers[1].

Currently, 20 genes have been reported to be associated with LIS, and many of them are microtubule genes[5,6]. In a cohort study of 811 patients with LIS, the overall mutation frequency of the entire cohort was 81%, of which LIS1 accounted for 40%, followed by DCX (23%), TUBA1A (5%), and DYNCHI (3%). Other genes accounted for 1% or less. Interestingly, the cause of LIS in 19% of the patients was unknown, which indicates that additional genes are involved and need to be discovered[6]. There have been no other reports of LIS caused by GPR56 gene mutations. Therefore, the relationship between LIS and GPR56 still needs further research.

There is no specific treatment method for LIS. Current treatments typically involve symptomatic relief, such as anti-epileptic treatment and rehabilitation training. Studies in animal models have shown that it might be possible to restart neuronal migration by re-expressing the missing/nonfunctional genes after birth[2]. Even if the degree of cortical deformity is partially improved, it may significantly decrease seizure frequency and clinical severity[2]. Therefore, with the advances in genetic testing and medical technology, the diagnosis and treatment of LIS will continue to be improved and optimized.
CONCLUSION

The compound mutations in the GPR56 gene identified in the twin sisters with LIS were novel and unreported mutations. This finding has broadened our knowledge of the clinical manifestations of LIS and increased our understanding of GPR56. Genetic testing is necessary when patients suffer from LIS symptoms.

ACKNOWLEDGEMENTS

We sincerely appreciate the patients and their parents for their help and willingness in this study.
Lin WX et al. GPR56 mutation in a twin infant with lissencephaly

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Patients with SERPINC1 rs2227589 polymorphism found to have multiple cerebral venous sinus thromboses despite a normal antithrombin level: A case report

Feng Liao, Jun-Ling Zeng, Jian-Gang Pan, Jing Ma, Zhi-Jian Zhang, Zhi-Jun Lin, Li-Feng Lin, Yu-Sen Chen, Xiao-Tang Ma

ORCID number: Feng Liao 0000-0003-4963-0778; Jun-Ling Zeng 0000-0002-9025-3321; Jian-Gang Pan 0000-0002-5693-2515; Jing Ma 0000-0002-0661-7373; Zhi-Jian Zhang 0000-0003-1205-5378; Zhi-Jun Lin 0000-0002-0734-0580; Li-Feng Lin 0000-0001-8741-6575; Yu-Sen Chen 0000-0002-8640-2849; Xiao-Tang Ma 0000-0002-0657-5556.

Author contributions: Liao F and Zeng JL contributed equally to this work; Liao F and Zeng JL wrote the manuscript; Pan JG, Ma J, Zhang ZJ, Lin ZJ and Lin LF performed the experiment and analyzed the data; Ma XT and Chen YS designed the research study and revised the manuscript; all authors have read and approved the final manuscript.

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

Conflict-of-interest statement: 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.

Abstract

BACKGROUND

The hereditary antithrombin (AT) deficiency caused by SERPINC1 gene mutation is an autosomal dominant thrombotic disorder. An increasing number of studies have shown that mutations in the SERPINC1 rs2227589 polymorphic site are correlated with a risk of venous thromboembolism (VTE) at common sites, such as lower extremity deep venous thrombosis and pulmonary thromboembolism. Currently, there are no reports of cerebral venous sinus thrombosis (CVST), a VTE site with a low incidence rate and rs2227589 polymorphism.

CASE SUMMARY

Here, we report a Chinese CVST case with a mutation of the SERPINC1 rs2227589 polymorphic site, which did not cause significant AT deficiency. In a 50-year-old male patient presenting with multiple cerebral venous sinus thromboses no predisposing factors were detected, although a relative had a history of lower extremity deep venous thrombosis. We performed sequencing of the SERPINC1 gene for the patient and his daughter, which revealed the same heterozygous mutation at the rs2227589 polymorphic site: c.41+141G>A.

CONCLUSION

The results showed that more studies should be conducted to assess the correlation between rs2227589 polymorphism and CVST.
Liao F et al. Case of multiple cerebral venous sinus thromboses

Key Words: Cerebral venous sinus thromboses; SERPINC1 rs2227589 polymorphic; Deep venous thrombosis; Venous thromboembolism; Case report

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Core Tip: The hereditary antithrombin (AT) deficiency caused by SERPINC1 gene mutation is an autosomal dominant thrombotic disorder. Currently, there are no reports on SERPINC1 rs2227589 polymorphism and cerebral venous sinus thrombosis (CVST). Here, we report for the first time a Chinese CVST case with a mutation of the SERPINC1 rs2227589 polymorphic site, which did not cause significant AT deficiency. More studies should be conducted to assess the correlation between rs2227589 polymorphism and CVST.

Citation: Liao F, Zeng JL, Pan JG, Ma J, Zhang ZJ, Lin ZJ, Lin LF, Chen YS, Ma XT. Patients with SERPINC1 rs2227589 polymorphism found to have multiple cerebral venous sinus thromboses despite a normal antithrombin level: A case report. World J Clin Cases 2022; 10(2): 618-624

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i2.618

INTRODUCTION
Thrombophilia refers to a tendency for pathological venous or arterial thrombosis caused by interactions between multiple genetic and/or acquired susceptibility factors [1]. Venous thromboembolism (VTE) is a typical hereditary thromboembolism, which is common in lower extremity deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) [2]. Cerebral venous sinus thrombosis (CVST) is a rare occurrence of VTE, with an incidence rate at least 25-50 times lower than that observed in common sites of VTE [3]. Common genetic risk factors for venous thrombosis include coagulation factor V and coagulation factor II, protein C and protein S, as well as mutations in the antithrombin (AT) gene [4]. The polymorphism of antithrombin gene SERPINC1 rs2227589 has been studied mostly in Caucasian people, where its association with the risk of DVT and recurrent pregnancy loss (RPL) has been demonstrated [5-7]. Studies on Chinese people have also reported an association with familial DVT, PTE, and coronary heart disease. However, no reports on rs2227589 polymorphism and CVST currently exist, due to the rarity of the symptom.

As a member of the serine protease inhibitor superfamily, AT is the most important anticoagulant molecule in the body and is involved in regulating thrombin, factor Xa, and other clotting factors [8]. Hereditary AT deficiency is caused by various SERPINC1 gene mutations and is a thrombotic disease of autosomal dominant inheritance [9]. AT deficiency increases the risk of first-onset VTE by about 16-fold and recurrent VTE by about four-fold. Additionally, an increasing number of studies have found that even AT levels near the lower limit of its normal range may increase the risk of VTE significantly [10,11].

Here, on the other hand, we report a CVST case with a mutation of the SERPINC1 rs2227589 polymorphic site, which did not result in significant AT deficiency.

CASE PRESENTATION

Chief complaints
A 50-year-old male patient was admitted to the emergency room after experiencing headache pain for 10 d.

History of present illness
Headache for 10 d.
History of past illness
The patient did not have a history of hypertension, diabetes, hyperlipidemia, surgery, infection, liver or kidney dysfunction, smoking or drinking. He was married.

Personal and family history
His grandfather had a history of venous thrombosis in the lower extremities.

Physical examination
The physical examination yielded the following results: body mass index = 21 kg/m², with stable vital signs, and clear consciousness. The patient's ophthalmoscopy indicated the presence of optic papilledema, normal results for the rest of the cranial nerves and for muscle tension of the extremities, limb muscle strength was rated as grade 5 based on the Medical Research Council scale, normal depth of feeling, normal tendon reflex, and negative Babinski, Chaddock, and meningeal irritation signs. The patient’s Montreal Cognitive Assessment was 29.

Laboratory examinations
The blood test results were as follows: D-dimer: 1430 g/L, prothrombin time: 16.3 s (reference range: 10.6-14.3 s), plasma partial thromboplastin time: 45.4 s (26.0-40.0 s), without obvious abnormalities on routine examinations of blood, urine, and feces, serum homocysteine concentration, anticardiolipin antibodies, rheumatic antineutrophil cytoplasmic antibodies, negative antinuclear antibodies, rheumatoid factors, thyroid function, erythrocyte sedimentation rate, and creatine kinase level.

To determine the reason for CVST, coagulation tests were performed. The results were as follows: AT activity: 81.8% (reference range: 75%-125%), protein C: 52.8%, protein S: 31.9% (reference range: 70%-140%), and LA1/LA2 for preliminary screening/diagnosis of lupus: 1.16 (reference range: 0.8-1.2) (Table 1). Because the patient had taken warfarin for one week for anticoagulation the anticoagulant protein test was performed. Warfarin is known to reduce the content and activity of plasma protein C and protein S antigens; hence, the drug was considered to be the reason for the observed decrease in activity of protein C and protein S. As the patient had no acquired risk factors for thrombophilia, such as surgery, immobilization, trauma, or infection, the possibility of hereditary thrombophilia was considered. Coagulation factor II, V, and SERPINC1 gene detection showed that the patient had no gene mutation of coagulation factor II and V, but had heterozygous mutations in the introns around Exon 1 (rs2227589 site) of SERPINC1 that encoded the AT gene: c.41+141G>A (Figure 1A).

Considering that the patient’s daughter was of childbearing age, we also conducted blood coagulation tests and SERPINC1 gene test for the patient's daughter, to determine whether thromboprophylaxis needed to be given during perinatal and contraceptive periods when the risk of VTE is increased. The results showed that her AT-III, protein C, and protein S were all normal (Table 1). SERPINC1 gene detection showed the same heterozygous mutations in the introns around Exon 1 (rs2227589 site) as her father: c.41+141G>A (Figure 1B).

Imaging examinations
The patient had an unexplained acute headache, with nausea, vomiting and intracranial hypertension with fundus optic papilledema. He had a family history of venous thrombosis and was highly vigilant against CVST. Subsequently, a brain magnetic resonance imaging (MRI) scan was performed. As expected, cranial magnetic resonance venography (MRV) and MRI revealed several abnormal findings: filling defects were observed in the superior sagittal sinus, inferior sagittal sinus, straight sinus, torcular herophili, bilateral sigmoid sinus, and transverse sinus (Figure 2), which enabled a diagnosis of multiple CVST.

MRV and MRI examination 2 wk later showed that the inferior sagittal sinus and straight sinus were significantly clearer than that before treatment, while the superior sagittal sinus, bilateral sigmoid sinus, and transverse sinus were slightly fuller than that before treatment (Figure 3).

Final Diagnosis
Cerebral venous sinus thromboses.
Table 1 Clinical phenotypes and coagulation test data of the patient and his daughter

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age</th>
<th>Clinical phenotype</th>
<th>AT activity, %</th>
<th>Protein C, %</th>
<th>Protein S, %</th>
<th>LA1/LA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>50</td>
<td>1 episode</td>
<td>81.8</td>
<td>52.8</td>
<td>31.9</td>
<td>1.16</td>
</tr>
<tr>
<td>Daughter</td>
<td>27</td>
<td>No thrombotic events</td>
<td>90.1</td>
<td>104.6</td>
<td>56.4</td>
<td>-</td>
</tr>
</tbody>
</table>

At the time of testing, the patient had been taking warfarin for 1 wk. AT: Antithrombin; LA1/LA2: Preliminary screening/diagnosis of lupus.

Figure 1 Sequence map illustrating the SERPINC1 gene mutation in the patient (A) and his daughter (B). The heterozygous mutation site (rs2227589 polymorphism site) of c.41+141G>A is marked by the black arrow.

Figure 2 Brain magnetic resonance imaging at admission. A: Filling defects seen in the superior sagittal sinus, bilateral transverse sinuses, and sigmoid sinus, indicated by magnetic resonance venography (MRV) are shown by arrows; B: Blurred image of the inferior sagittal sinus and straight sinus, indicated by MRV are shown by arrows; C: Thrombosis of the superior sagittal sinus, indicated by magnetic resonance imaging is shown by the arrow.

TREATMENT

The treatment regimen included a subcutaneous injection of 4100U nadroparin calcium, q12h. The headache was relieved and relevant conditions were stable. After 3 d, warfarin was administered orally for anticoagulation at a dose of 2.5 mg, q.d., with
the international normalized ratio (INR) maintained between 2.0 and 3.0.

OUTCOME AND FOLLOW-UP
MRV and MRI examination 2 wk later showed that the inferior sagittal sinus and straight sinus were significantly clearer than before treatment, while the superior sagittal sinus, bilateral sigmoid sinus, and transverse sinus were slightly fuller than before treatment.

DISCUSSION
Single nucleotide polymorphisms (SNPs) are the least complex mutations and are caused by the variation of a single nucleotide at the DNA level\[13]. Although they usually have no effect on human health, they may affect the expression or stability of mRNA, resulting in medical impairment in 24% of cases when located at the transcription factor binding site or the non-translational region of the mRNA\[7].

rs2227589 is an SNP site on introns near the AT gene SERPINC1 in Exon1. After evaluation of 19,682 SNP sites on 10887 genes in three controlled studies, Bezemer et al\[7] first proposed that the rs2227589 polymorphism in the SERPINC1 gene was associated with DVT formation (OR: 1.29, 95%CI: 1.10-1.49). In a study of a normal Spanish cohort, Anton et al\[14] confirmed that in SERPINC1 rs2227589 mutation carriers, AT activity (94.6 ± 8.4%) and levels (94.8 ± 5.6%) were also slightly reduced, possibly explaining the functional effect of the rs2227589 polymorphism. The correlation between the rs2227589 polymorphism and VTE risk has been shown to vary between ethnic groups. On the other hand, a systematic analysis of multiple groups by Yue et al\[15] showed that rs2227589 and VTE were significantly correlated in the additive (OR: 1.09, 95%CI: 1.08-1.18) and dominant (OR:1.10, 95%CI: 1.01-1.20) genetic models. Therefore, we conclude that a mutation at the SERPINC1 rs2227589 site is a predisposing factor for CVST.

The AT level was 81.8% (normal range: 75%-125%) in this patient. Although the AT level fell within the normal range, a controlled study on a large number of VTE cases stratified by AT level showed that an AT level around the lower limit of its normal range (76%-85%) increases the risk of VTE by two-fold\[11]. We think that the increase in risk contributed to the patient’s CVST.

The latest European Academy of Neurology - European Stroke Organization guide for treatment of adult patients with CVST suggested that relevant patients without contraindications should be given anticoagulation treatment as soon as possible, with low molecular weight heparin given in the acute phase, and then warfarin administered orally for further anticoagulation according to an INR controlled within 2.0-3.0. The duration of treatment depends on thrombophilia and the risk of its recurrence\[16]. Based on the medical history and relevant examination results of this patient, we first adopted 3 d of treatment with Nadroparin calcium during hospital-
ization, and then changed to oral warfarin for further anticoagulation. The dose was gradually increased, with the INR monitored and controlled between 2.0 and 3.0. A head MRI reexamination 2 wk later indicated partial thrombolysis and significant relief of headache symptoms. Therefore, the treatment was effective.

For the patient’s daughter, the AT level was 90.1%. Relevant studies have confirmed that the AT level is negatively correlated with age[17], and the risk for first-onset venous thrombosis may increase with a decrease in AT levels[10]. We speculate, therefore, that the asymptomatic condition of the patient’s daughter may be due to a relatively high AT level and low risk of VTE, and relatively old age expected for her first-onset VTE.

Prevention of VTE during pregnancy among women with genetic risk factors for thromboembolism is a challenge. The American College of Obstetricians and Gynecologists (ACOG) guide (2018) indicates the likelihood of synergistic effects between homozygous FVL, compound heterozygous FVL and PT20210A, AT deficiency, and high estrogen status, which are high genetic risk factors for thrombophilia[18]. The patient’s daughter was a rs2227589 polymorphic site mutation carrier without serious AT defects at this stage. Considering that existing data on rs2227589 research are limited, we consider similar conditions to be low risk for hereditary thrombophilia. For these patients, with first-degree relatives who have a family history of VTE, the ACOG recommends only prenatal monitoring without anticoagulant therapy or prophylactic use of heparin and, after delivery, the use of anticoagulant therapy or moderate heparin dosage to prevent thrombosis. Estrogen-containing drugs may increase the risk of VTE[19]. We recommend the use of a condom for contraception for the patient’s daughter if necessary.

CONCLUSION

To sum up, most studies of rs2227589 polymorphisms have investigated the risk of VTE at common sites of VTE, but have not studied the risk of rs2227589 polymorphism for CVST due to the rarity of CVST at the more common VTE sites. We report a case of CVST with a mutation of SERPINC1 at the rs2227589 polymorphic site, which did not exhibit significant AT deficiency. Therefore, further studies are needed to confirm the correlation between rs2227589 polymorphism and CVST, as well as ongoing exploration to identify new genetic risk factors related to CVST. In addition, the mutation of the rs2227589 special site only led to a slight decrease in AT level in this patient, suggesting that serious CVST can still occur even when the AT level is in the normal range. This report illustrates that when severe CVST occurs and common reasons for thrombosis are not identified, the possibility of rs2227589 polymorphism site variation should be considered if the AT level is slightly lower but still in the normal range.

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Successful management of delirium with dexmedetomidine in a patient with haloperidol-induced neuroleptic malignant syndrome: A case report

Chi-Ju Yang, Ching-Tang Chiu, Yu-Chang Yeh, Anne Chao

Abstract

BACKGROUND
We report a case of lorazepam-induced agitated delirium treated with haloperidol, which in turn triggered the onset of neuroleptic malignant syndrome (NMS). The latter condition, a medical emergency, was effectively treated with medical treatment and dexmedetomidine, a versatile and highly selective short-acting alpha-2 adrenergic agonist with sedative-hypnotic and anxiolytic effects.

CASE SUMMARY
A 65-year-old man with a history of bipolar disorder presented to the emergency department with severe abdominal discomfort after binge eating. During his hospital stay, he received intravenous lorazepam for insomnia. On the next day, he became delirious and was thus treated with seven doses (5 mg each) of haloperidol over a 48 h period. Signs of NMS (hyperthermia, rigidity, myoclonus of upper limbs, impaired consciousness, tachypnea, and dark urine) became apparent and haloperidol was immediately suspended and brisk diuresis was initiated. On intensive care unit admission, he was confused, disoriented, and markedly agitated. Dexmedetomidine infusion was started with the goal of achieving a Richmond Agitation-Sedation Scale score of -1 or 0. NMS was resolved gradually and the patient stabilized, permitting discontinuation of dexmedetomidine after 3 d.

CONCLUSION
Dexmedetomidine may be clinically helpful for the management of NMS, most likely because of its sympatholytic activity.
Delirium, a transient, reversible organic mental syndrome characterized by disorganized thinking and altered consciousness, commonly occurs in acutely hospitalized elderly patients[1]. Hospital-acquired delirium can be triggered by certain drugs administered upon admission or during the patient’s stay, including benzodiazepines[2]. While haloperidol is a commonly accepted first-line treatment against agitated delirium[3], the risk of serious adverse events is not negligible. Among them, neuroleptic malignant syndrome (NMS), a life-threatening condition characterized by hyperthermia, severe muscle rigidity, altered mental status, and autonomic dysfunction, can occur in 0.02%–3% of all patients who receive haloperidol[4]. The clinical management of NMS poses major challenges, but intensive care unit (ICU) medications are emerging as part of the therapeutic armamentarium[5].

Herein, we report a case of lorazepam-induced agitated delirium treated with haloperidol, which in turn triggered the onset of NMS. The latter condition, a medical emergency, was effectively managed with medical treatment and dexmedetomidine, a versatile and highly selective short-acting alpha-2 adrenergic agonist with sedative-hypnotic and anxiolytic effects. Dexmedetomidine may be clinically helpful for the management of NMS because of its sympatholytic activity. In the presence of rapid shallow breathing, dexmedetomidine may provide better patient comfort with less respiratory depression than does propofol.

**Case Presentation**

**Chief complaints**
A 65-year-old man presented to the emergency department with severe abdominal discomfort after binge eating.

**History of present illness**
Because of food impaction, oral intake and medications were discontinued. However, lorazepam was administered intravenously to treat insomnia. The next day, the patient became delirious and was thus treated with seven doses (5 mg each) of haloperidol over a 48 h period. Unfortunately, he developed hyperthermia (body temperature: 40.6 °C) accompanied by tachypnea (respiratory rate: 40 breaths per min), tachycardia (heart rate: 128 beats per min), impaired consciousness, muscle rigidity, and dark...
urine. The serum creatine kinase (CK) levels were markedly increased (1910 U/L) (Figure 1), indicating rhabdomyolysis. NMS was diagnosed, and haloperidol was immediately stopped. Adequate hydration and body cooling were implemented; additionally, bromocriptine (2.5 mg/3 times daily) and transdermal patches containing rotigotine (2 mg/24 h) were applied to overcome the hypodopaminergic state. The patient was subsequently transferred to the ICU for intensive monitoring and treatment of NMS.

**History of past illness**
The patient’s medical history was notable for bipolar disorder, and his medications included trihexyphenidyl, quetiapine, flupentixol, and flunitrazepam.

**Personal and family history**
Bipolar disorder.

**Physical examination**
Upon initial evaluation, the patient’s temperature was 36 °C, the heart rate 102 beats per min, and the respiratory rate 20 breaths per min. A physical examination revealed abdominal tension.

**Laboratory examinations**
The laboratory findings upon ICU admission were as follows: CK, 21000 U/L; blood urea nitrogen, 29 mg/dL; creatinine, 1.4 mg/dL; potassium, 4.5 mEq/L; blood pH, 7.4; PCO₂, 31 mmHg; PO₂, 70 mmHg; HCO₃⁻, 23 mEq/L; and base excess, -1.5 mmol/L.

**Imaging examinations**
Computed tomography revealed food impaction accompanied by bowel distension from the esophagus to the small intestine (Figure 2).

**FINAL DIAGNOSIS**
Lorazepam-induced delirium treated with haloperidol, which in turn triggered NMS.

**TREATMENT**
On ICU admission, the patient was confused and disoriented to time, space, situation, and persons. His Glasgow coma score (GCS) was 13 (Eye 4, Motor 5, and Verbal 4) and papillary light reflexes were bilaterally positive. Severe rigidity and myoclonus (especially in the upper extremities) were evident. Additionally, the patient was severely agitated (Richmond Agitation-Sedation Scale (RASS)[9] score = 3), and made attempts at removing his intravenous catheter and nasogastric tube. In addition to continuation of medical management, dexmedetomidine infusion was started (initial rate: 0.2 µg/kg/h) with the goal of achieving a RASS score of -1 or 0. Owing to persistent agitation (accompanied by shouting and attempts to remove restraints), dexmedetomidine dosing was further increased to 0.5 µg/kg/h. Gradual resolution of muscle rigidity, myoclonus, and agitation was observed over the next day (GCS score: 14). Thus, the dosage of dexmedetomidine was lowered to 0.3 µg/kg/h. The family’s presence at the patient’s bed side was encouraged. Containment measures were removed and the dexmedetomidine dosing was further reduced. Full cooperation was achieved 72 h after the initial infusion of dexmedetomidine, which was thus discontinued. After full regression of rhabdomyolysis and rigidity, the patient was transferred to the general ward for further care. Figure 3 depicts the timeline of the main clinical events.

**OUTCOME AND FOLLOW-UP**
The patient did not present additional episodes of delirium and was successfully discharged 18 d after admission. He is currently undergoing regular follow-up at our psychiatric clinic.
We describe a complex case of lorazepam-induced delirium occurring in an elderly hospitalized patient who was admitted for food impaction. Treatment of delirium with haloperidol precipitated the onset of NMS, an uncommon, yet life-threatening, complication of antipsychotics. Early diagnosis and removal of precipitating agents are very important in the management of NMS. NMS was managed with dexmedetomidine, an ICU drug, which successfully corrected autonomic instability. Clinical improvement was observed within a few days and the patient was successfully discharged 18 d after admission. Our case provides an illustrative example of how
polypharmacotherapy in acutely hospitalized elderly patients can give rise to medical emergencies requiring ICU care.

Benzodiazepines are a common cause of drug-induced delirium. In the elderly, because of the decreased renal clearance and other age-related pharmacodynamic and pharmacokinetic changes, these drugs can accumulate and cause toxicity and delirium [10]. Our patient became delirious after in-hospital administration of lorazepam for insomnia. Although the mechanisms of benzodiazepine-induced delirium are not well defined, neurotransmitter imbalances with excess brain dopaminergic activity are common in delirious patients [10,11]. Importantly, while medications can induce delirium, they may also be used to manage its symptoms [10]. Owing to their antipsychotic effects, typical antipsychotics like haloperidol are commonly used in managing delirium [3]. As in our patient, haloperidol can be given at multiple doses (2–5 mg every 15–30 min) until clinical improvement is achieved [12]. However, the use of haloperidol for managing delirium in our case precipitated the onset of NMS, possibly as a result of excess dopamine D<sub>2</sub> receptor blockade in the hypothalamic, nigrostriatal, mesolimbic, and mesocortical pathways [13].

Once NMS is diagnosed, ICU drugs like dexmedetomidine or propofol are potentially effective management options [14,15]. Because extreme sympathetic nervous system activation is involved in the pathophysiology of NMS [7], we reasoned that dexmedetomidine may be helpful in the management of this medical emergency because of its sympatholytic activity [8]. In the presence of rapid shallow breathing as in our case, dexmedetomidine may also provide better patient comfort with less respiratory depression than does propofol [16]. Importantly, dexmedetomidine also suppresses the spontaneous firing rate of locus coeruleus neurons and decreases heat generation by alpha-2 adrenergic receptor blockade in the hypothalamic, nigrostriatal, mesolimbic, and mesocortical pathways [17].

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**CONCLUSION**

Dexmedetomidine may be clinically beneficial for managing NMS because of its sympatholytic activity and its capacity to reduce heat generation. In the presence of rapid shallow breathing, dexmedetomidine may also provide better patient comfort.
with less respiratory depression than does propofol.

REFERENCES


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Malignant solitary fibrous tumor in the central nervous system treated with surgery, radiotherapy and anlotinib: A case report

Dong-Yong Zhang, Lan Su, Yi-Wei Wang

Abstract

BACKGROUND
Solitary fibrous tumor (SFT) of the central nervous system is rare. It is predominantly benign and rarely malignant. There is no established standardized treatment regimen for malignant intracranial SFTs.

CASE SUMMARY
We present a rare case of SFT in a 9-year-old girl with a space-occupying effect in the frontal-parietal lobes. She underwent craniotomy, and the mass was resected. Immunohistochemistry examination of the specimen showed that Ki-67 proliferation index staining was highly positive in 80% of tumor cells. Whole exome sequencing of the surgical tissue showed 38 somatic gene mutations and 1 gene amplification such as fibroblast growth factor receptor 4 or TP53. At 1.5 mo after surgery, head magnetic resonance imaging revealed that the tumor had recurred. The patient received 60 Gy and 30 fractions of intensity modulated radiotherapy. The patient then received anlotinib 8 mg po qd for 1-14 d of a 21 d cycle. Following this regimen, the patient achieved stable disease for >17 mo. Magnetic resonance imaging at 1.5 year after surgery showed that the tumor had not progressed.

CONCLUSION
This is the first reported case of SFT of the central nervous system treated with surgery, radiotherapy and anlotinib. This regimen may be an effective treatment option for malignant intracranial SFT patients.

Key Words: Anlotinib; Biological therapy; Mutation; Recurrence; Sequence analysis; Case
Zhang DY et al. Malignant intracranial solitary fibrous tumor

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Core Tip: Solitary fibrous tumor (SFT) of the central nervous system is rare. There is no established standardized treatment regimen for malignant intracranial SFTs. This is the first reported case of SFT in the central nervous system treated with surgery, radiotherapy and anlotinib. This treatment regimen might be an effective treatment option for malignant intracranial SFT patients.

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INTRODUCTION

Solitary fibrous tumor (SFT) is a rare soft tissue tumor of mesenchymal cell origin. An SFT mainly develops in the pleural cavity, but it can arise in a variety of non-pleural soft tissue sites throughout the body. The incidence of SFT in the central nervous system (CNS) is very low and usually originates from the cranial meninges. The NGFI-A-binding protein (NAB2) and signal transducer and activator of transcription (STAT6) gene fusion was identified as a driver mutation of SFT. Based on SFT and hemangiopericytoma (HPC) containing identical genetic abnormalities, they were considered a new combined entity in the 2016 CNS classification[1]. This classification described three grades of SFT/HPC, grade I, grade II and grade III. The first case of intracranial SFT was described by Carneiro[2] in 1966. This tumor most commonly affects adults and is generally benign in the CNS[3]. Malignant SFT of the CNS is exceedingly rare.

No standardized treatment guideline is available for malignant intracranial SFTs. The main treatments are surgical resection and postoperative radiotherapy. Despite the combination of surgery and adjuvant radiotherapy, the control rates of malignant SFT have been disappointing. Targeted therapy for the treatment of the soft tissue tumors has been developed recently. Anlotinib (Chia-tai Tianqing Pharmaceutical Co., Ltd, China) is a newly multitargeted tyrosine kinase inhibitor with anti-neoplastic and anti-angiogenic activities. It inhibits tumor angiogenesis and proliferation. There are ongoing phase I/II/III clinical trials of anlotinib for different carcinomas and sarcomas in China and other countries. To our knowledge, there are no studies on anlotinib for the treatment of intracranial SFT. In this report, we present a girl with intracranial SFT who was effectively treated by surgery, radiotherapy and anlotinib. We discuss the histopathological features, next-generation sequencing results and anlotinib treatment of cancer, together with a brief review of the literature on SFT treatment by monotherapy.

CASE PRESENTATION

Chief complaints
A 9-year-old girl presented to our hospital emergency department with a 3-wk history of ineffective right limb movement.

Imaging examinations
The treatment timeline is shown in Figure 1A. A head computed tomography (CT) scan revealed a quasi-circular mass in the left frontal-parietal region with high-density and associated hemorrhage (Figure 1B). Brain magnetic resonance imaging (MRI) revealed low signals on T1 weighted imaging with high surrounding signals. High signals on T2 weighted imaging with low surrounding signals were observed, with
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Figure 1 Treatment timeline and radiography. A: The treatment timeline. B: A head computed tomography scan revealed a quasi-circular mass in the left frontal-parietal region with high-density and associated hemorrhage. Brain magnetic resonance imaging (MRI) revealed low signals on T1 weighted imaging with high surrounding signals. High signals on T2 weighted imaging with low surrounding signals were observed, with marked enhancement on contrast measuring 4.8 cm × 5.0 cm × 4.5 cm in the left motor area of the frontal-parietal lobes (axial, sagittal and coronal views); C: Gadolinium-enhanced MRI imaging in axial, sagittal and coronal views 1 mo after surgery. MRI imaging showed no residual tumor. 1.5 mo after surgery, MRI imaging showed a solid mass. Five months and 1.5 year after surgery, MRI imaging showed that the tumor had not progressed. MRI + C: Gadolinium-enhanced magnetic resonance imaging.

marked enhancement on contrast measuring 4.8 cm × 5.0 cm × 4.5 cm in the left motor area of the frontal-parietal lobes (Figure 1B). The imaging characteristics were similar to meningioma. An unenhanced chest CT scan revealed no nodules in the chest.
Laboratory examinations
Laboratory tests including complete blood cell counts, bleeding time, activated partial thromboplastin time, prothrombin time, liver and renal function and blood glucose level were within normal ranges.

Physical examination
Her temperature was 36.6 °C, resting respiratory rate was 16 breaths/min, heart rate was 90 bpm and blood pressure was 120/75 mmHg. Neurological examination showed that her Glasgow Coma Scale score was 15 (E4V5M6), and muscle strength was grade 2 in the right limbs. She did not have any other neurological deficits.

Personal and family history
She had no personal or family history of benign or malignant tumors.

History of past illness
The patient had no history of prior illness.

History of present illness
The patient had ineffective right limb movement for 3 wk. She also had headaches, accompanied by nausea and vomiting and excess sleep. A head CT scan revealed a quasi-circular mass in the left frontal-parietal region with high-density and associated hemorrhage.

MULTIDISCIPLINARY EXPERT CONSULTATION
Examination of a frozen section of the biopsy revealed features of malignant tumor. Hematoxylin and eosin staining showed that a large number of spindle or oval cells were diffusely distributed, with deep staining of a null, “staghorn” vascular pattern, hypercellularity and increased mitotic activity were observed in the tumor (> 4 mitosis/10 high-power fields) (Figures 2A and B). Immunohistochemistry examination of the specimen showed positivity for CD99, Bcl-2, TP53, IDH1, TLE-1 and vimentin (Figures 2C-2H) and negativity for CD34, STAT6, CK, EMA, Olig2, PR, SSTR2, CD68, S-100 and GFAP (Figures 2J-2L). Ki-67 proliferation index staining was highly positive in 80% of tumor cells (Figure 2I). Based on the above findings, the pathological diagnosis of malignant SFT was confirmed. The patient’s parents sent the specimen to the Department of Neuropathology, Beijing Neurosurgical Institute to confirm the diagnosis. The pathological diagnosis concurred with that at our hospital. The primary surgical tissue was subjected to whole-exome sequencing by next-generation sequencing (Genetron Health Co., Ltd, Beijing, China). A global landscape of gene mutations was generated from the whole exome sequencing data (Figure 3). A total of 38 somatic gene mutations, including 36 missense mutations, 2 frameshift mutations and 1 gene amplification were detected. These gene alterations were divided into: genes related to chemotherapy and targeted drug-related genes. In targeted drug-related genes, fibroblast growth factor receptor (FGFR) 4 (c.1463G > A, p.Gly488Asp) and TP53 (c.751A > T, p.Ile251Phe) were detected (Table 1). However, this test did not reveal any gene fusion, especially NAB2-STAT6 gene fusion.

FINAL DIAGNOSIS
The patient was diagnosed with malignant SFT.

TREATMENT
The patient underwent left craniotomy under general anesthesia, and the mass was resected. After surgery, her motor examination showed improvement in the right limb, and she could walk unaided. Head MRI was performed 1 mo after surgery, and the results showed no residual tumor (Figure 1C). The patient was advised to undergo adjuvant radiotherapy due to high Ki-67, and MRI (1.5 mo after surgery) before radiotherapy planning showed a solid mass, suggesting a progressive tumor (Figure 1C). The patient was unable to walk by herself, and physical examination
showed muscle strength was grade 3 in the right limbs. The patient received 60 Gy and 30 fractions of intensity modulated radiotherapy. Mannitol was administered to relieve her symptoms by reducing intracranial pressure. After 19 d of radiotherapy, the patient could walk unaided. Considering her pathological diagnosis, FGFR4 and

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</table>

Table 1 Mutations of the specimen
TP53 mutation and progression of the disease, the oncologist at Beijing Cancer Hospital advised the patient to undergo anlotinib treatment. She received anlotinib 8 mg po qd for 1-14 d of a 21 d cycle at home 3 mo after surgery. During anlotinib treatment, the patient occasionally suffered from loss of appetite, and her laboratory results were within the normal range. MRI performed 5 mo after surgery showed that the tumor had not progressed (Figure 1C). The patient took anlotinib orally for 17 mo.
OUTCOME AND FOLLOW-UP

Follow-up MRI showed that the tumor had not progressed 1.5 years after surgery (Figure 1C). An unenhanced chest CT scan revealed no nodules in the chest.

DISCUSSION

We present the first known case of malignant intracranial SFT treated with surgery, adjuvant radiotherapy and anlotinib, leading to a good prognosis. SFT is a rare soft tissue tumor in the CNS. The first case of SFT in the CNS was described by Carneiro[2] in 1966. SFT most commonly affects adults and is generally benign. A few cases have been described in children. An MRI scan 1 mo after surgery showed that the tumor had been successfully resected in our case. However, 2 wk after the first MRI examination, the tumor rapidly progressed as shown by head MRI in this 9-year-old patient. The immunohistochemical features of intracranial SFT and HPC overlap. They share an inversion at 12q13 fused with NAB2 and STAT6 genes, and the combined term is “SFT/HPC”[1]. This classification described three grades of SFT/HPC, grade I-III. Grade I was previously diagnosed as SFT. Grade II was previously diagnosed as CNS HPC. Grade III was previously termed anaplastic HPC and malignant SFT. Our patient had grade III CNS SFT and had a poor prognosis. However, disease progression was controlled following her treatment regimen.

The nuclear expression of STAT6 on immunohistochemistry is very important in the pathological diagnosis of SFT[4,5]. Although NAB2-STAT6 fusion seems to be important in the diagnosis of SFT, its detection may be difficult unless high-throughput sequencing is performed to detect breakpoints. Most SFTs have shown NAB2-STAT6 fusion, and the remaining 11% of cases lacked an identifiable NAB2-STAT6 fusion[3]. Our case did not show NAB2-STAT6 fusion following high-throughput sequencing, and no nuclear STAT6 expression was observed on immunohistochemical analysis. Hematoxylin and eosin staining showed a high-grade component mimicking a spindle cell sarcoma, small-cell sarcoma and other entities that have no morphological resemblance to SFT. The dedifferentiation of SFT can induce the loss of STAT6 expression on immunohistochemistry[6-8]. We speculated that Ki-67 proliferation index was 80%, and the tumor was highly dedifferentiated.
which suggest the reasons for negative STAT6 on immunohistochemistry. Although STAT6 is a sensitive marker in the diagnosis of SFT, other immunohistochemical indices, such as CD99, Bcl-2 and vimentin are also sensitive markers for the diagnosis of intracranial SFT[9-11]. Han et al.[12] analyzed 53 cases using immunohistochemistry and found that CD99 was positive in 94.3% of cases and Bcl-2 was positive in 96.2% of cases.

The differential diagnosis of SFT in the CNS includes meningioma. MRI initially showed that the mass was broadly attached to the dura matter in our patient. However, the dural tail sign, which is the most important characteristic of meningioma on MRI, was absent. Secondly, EMA and SSTR2 were negative in our case by immunohistochemistry, as opposed to meningioma in which EMA and SSTR2 are both positive[13]. Thirdly, meningioma is usually a benign tumor, and SFT tends to be aggressive. In our case, Ki-67 proliferation index was 80% and showed that the tumor was very malignant. These features can be used to differentiate SFT from meningioma.

As our patient was young, a diagnosis of synovial sarcoma was considered. The diagnosis of synovial sarcoma depends on the cytogenetic change t(X;18) (p11; q11), which is detected by fluorescence in situ hybridization assay[14]. In our case, fluorescence in situ hybridization assay showed that the t(X;18) was negative. Thus, the diagnosis in our patient was not synovial sarcoma. Another differential diagnosis we considered was schwannoma. However, the tumor was located in the frontal-parietal lobe, not the area where the cranial nerves are located. Therefore, a schwannoma was ruled out.

A malignant SFT has been shown to be hypercellular, mitotically active (> 4 mitosis/10 high-power fields), with cytological atypia, tumor necrosis and/or infiltrative margins[15]. Although our case did not show NAB2-STAT6 fusion following high-throughput sequencing and STAT6 expression on immunohistochemistry, CT scanning, MRI imaging, morphologic examination, conventional immunohistochemistry (positive for CD99, Bcl-2 and vimentin), high Ki-67 proliferation index and the exclusion of other tumors resulted in the diagnosis of malignant SFT.

SFT is frequently benign and if gross total resection is performed, it will not recur. HPC tends to be an aggressive tumor with the potential for local recurrence and metastases[16]. Although gross total resection offers a potential cure, improvement or preservation of motor function is crucial for patients. During surgery, we found that the tumor invaded the arachnoid, and gross total resection could cause the damage to the underlying cortex. Thus, gross total resection was not performed in our patient. Her muscle strength after surgery was better than that before surgery, and she could walk unaided. However, the disadvantage of this surgical method is that the tumor can recur. MRI (1.5 mo after surgery) showed a solid mass on the cut margin. SFT after subtotal resection has a high risk of local recurrence[17], and adjuvant radiation may be beneficial in some cases[18]. Rana et al.[19] analyzed 155 intracranial SFT patients and found that adjuvant radiation did not prolong overall survival time compared with the surgery group. However, Bishop et al.[20] found that the treatment of SFT with combined surgery and radiotherapy led to excellent local control. Therefore, the role of radiotherapy in SFT is still unclear. Due to the low number of patients, it is difficult to conduct high-quality clinical trials on this treatment regimen.

The tumor location in our case was in the motor area, and gross total resection of the tumor while preserving neurological function was relatively difficult. Head MRI 1 mo after surgery showed that the tumor had been successfully resected. However, 2 wk after the first MRI examination, brain MRI revealed tumor recurrence. The patient was advised to undergo adjuvant radiotherapy due to a high Ki-67 index and rapid recurrence. The patient received 60 Gy and 30 fractions of intensity modulated radiotherapy. After 20 d of radiotherapy, her limb weakness improved. We speculated that there were three main reasons for rapid alleviation of the patient’s symptoms. The first is that the time for the tumor to press against the motor zone of the cortex was relatively short and did not cause necrosis of cortical cells. Radiotherapy induces tumor cell necrosis, and the functions of these cells are then restored. The second is that we administered mannitol to relieve symptoms by reducing intracranial pressure. The third is that the tumor was more sensitive to radiotherapy, and it was effectively controlled. Our patient showed that radiotherapy resulted in excellent local control of intracranial malignant SFT.

Activation of oncogenes is a key mechanism of tumorigenesis and generally arises from a genetic mutation or amplification. As the therapeutic value of the genetic mutation depends heavily on the clinical prognosis, proving their direct involvement in personal targeted therapy has become a task for doctors. However, the extent of genetic intratumoral heterogeneity in SFTs is largely unknown. In our study, next-generation sequencing analysis showed significant germline aberrations and somatic
Table 2 Retrospective analyses of intracranial SFT treated with monotherapy

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Yr</th>
<th>Number of participants</th>
<th>CNS</th>
<th>Drug</th>
<th>RECIST</th>
<th>Choi</th>
<th>Median PFS in mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al[22]</td>
<td>2011</td>
<td>14</td>
<td>6</td>
<td>Temozolomide + bevazuzmab</td>
<td>2</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Stacchiotti et al[23]</td>
<td>2012</td>
<td>35</td>
<td>6</td>
<td>Sunitinib</td>
<td>2</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Valentin et al[24]</td>
<td>2013</td>
<td>5</td>
<td>1</td>
<td>Sorafenib</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Maruzzo et al[25]</td>
<td>2015</td>
<td>13</td>
<td>NA</td>
<td>Pazopanib</td>
<td>1</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Ebata et al[26]</td>
<td>2018</td>
<td>9</td>
<td>2</td>
<td>Pazopanib</td>
<td>0</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Martin-Broto et al[27]</td>
<td>2019</td>
<td>36</td>
<td>5</td>
<td>Pazopanib</td>
<td>2</td>
<td>21</td>
<td>18</td>
</tr>
</tbody>
</table>

RECIST: Response Evaluation Criteria in Solid Tumors; Choi: Choi response criteria; PR: Partial response; SD: Stable disease; PFS: Progression-free survival; NA: Not available.

point mutations were identified in hotspot cancer-related genes in this patient, such as FGFR4 and TP53.

Anlotinib, a newly designed oral small-molecule receptor tyrosine kinase inhibitor, was developed independently by Chia-Tai Tianqing Pharmaceutical Co., Ltd. in China. This drug was approved by the China Food and Drug Administration for the treatment of non-small cell lung cancer, soft tissue sarcoma, metastatic renal cell carcinoma and medullary thyroid cancer[21]. Anlotinib inhibits tumor angiogenesis and proliferation, targeting vascular endothelial growth factor, FGFR, platelet-derived growth factor α/β and c-KIT[21]. Several prospective studies suggest the potential efficacy of antiangiogenic treatments in SFT[22-27] (Table 2). Our patient received anlotinib 8 mg po qd for 1-14 d of a 21 d cycle after adjuvant radiotherapy for 17 mo. The follow-up MRI showed that the tumor had not progressed.

Oncogene alterations are present in all FGFR family members in human cancers. FGFR is a receptor tyrosine kinase consisting of an intracellular tyrosine-kinase domain and an extracellular ligand-binding domain. FGFR 1-3 often occur in amplifications or fusions in some cancers. However, FGFR 4 is infrequently mutated in cancers[28]. FGFR 4 mutations are present in 6% of melanomas[29]. One recent report found that 7% of cancers had FGFR aberrations, and FGFR 4 mutation was found in 0.5% of 4853 tumors[30]. Y367C mutation of the FGFR 4 gene in the breast cancer cell line MDA-MB453 promoted tumor growth[31]. Futami et al[32] identified FGFR 4 mutation in one of 83 gastric tumor specimens, and cells expressing this mutation showed a malignant phenotype. Multi-targeted tyrosine kinase inhibitors can be used to inactivate FGFR 4 by disrupting ATP binding in its tyrosine kinase domains[33]. Potential mechanisms of FGFR 4 activation include FGFR 4 overexpression and somatic mutations[34]. Therefore, we speculated that FGFR 4 mutation was likely to be the “driver” mutation and resulted in increased FGFR signaling in this patient. FGFR 4 mutation might be a key anticancer target for anlotinib in the treatment of malignant intracranial SFT.

TP53 is a tumor suppressor gene and plays a crucial role in malignant tumor progression. There is mounting basic and clinical evidence to show that tumors with TP53 gene mutations have a better response to antiangiogenic drugs than TP53 wild-type tumors[35]. Recent research found that anlotinib induced apoptosis in TP53 D259Y and R248G mutants, which were able to induce apoptosis through their transcription-independent function[36]. Fang et al[37] identified three cases with TP53 mutations (p.S183X on exon 5, p.S241F on exon 7, p.R175H on exon 5, K320fs on exon 9) that might represent biomarkers for predicting the effects of anlotinib in non-small cell lung cancer. Wu et al[38] reported a patient with pulmonary artery sarcoma harboring a TP53 mutation (p.R110P in exon 4) who had a favorable response to anlotinib. Kurisaki-Arakawa et al[39] found dedifferentiated SFTs in the pelvis with a TP53 mutation (p.A158H in exon 5). Morimitsu et al[40] found the TP53 mutation p.A116T in 1 of 17 cases with solitary extrapleural fibrous tumors. These findings suggest that various mutations of TP53 in SFTs are common, and tumors with TP53 mutations are more likely to respond to anlotinib. Based on the next-generation sequencing analysis, we speculated that TP53 mutation also plays a very important role in malignant SFT of the CNS treated with anlotinib monotherapy.
CONCLUSION

There is currently no standard treatment regimen for malignant SFT of the CNS. There is no effective targeted drug that can improve the prognosis of malignant intracranial SFT. This is the first report in the world of a patient with malignant intracranial SFT treated with surgery, radiotherapy and anlotinib monotherapy. Based on preliminary data, we speculated that FGFR 4 and TP53 mutations might be beneficial in the treatment of malignant intracranial SFT with anlotinib. Basic research and larger, randomized controlled trial are needed to confirm the results of the present study.

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Zhang DY et al. Malignant intracranial solitary fibrous tumor


CASE REPORT

Anesthesia and perioperative management for giant adrenal Ewing’s sarcoma with inferior vena cava and right atrium tumor thrombus: A case report

Ji-Lian Wang, Chuan-Ya Xu, Chun-Jing Geng, Lei Liu, Ming-Zhu Zhang, Hua Wang, Ruo-Tao Xiao, Lu Liu, Geng Zhang, Cheng Ni, Xiang-Yang Guo

ORCID number: Ji-Lian Wang 0000-0002-2812-5708; Cheng Ni 0000-0002-6104-423X.

Author contributions: Wang JL, Ni Cheng, Geng CJ, Liu L (Lei Liu), Wang H, Xiao RT, Liu L (Lu Liu) and Zhang G participated in patient care, data collection and manuscript draft; Ni C, Xu CY, Zhang MZ and Guo XY contributed to data analysis and manuscript revision; all authors have read and approved the final manuscript.

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Conflict-of-interest statement: The authors report no conflicts of interest in this work.

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Abstract

BACKGROUND

Ewing’s sarcoma of the adrenal gland with inferior vena cava (IVC) and right atrium thrombus is extremely rare. Here, we report a case of giant adrenal Ewing’s sarcoma with IVC and right atrium tumor thrombus and summarize the anesthesia and perioperative management.

CASE SUMMARY

A young female was admitted to the Department of Urology with intermittent pain under the right costal arch for four months. Enhanced abdominal computed tomography revealed a large retroperitoneal mass (22 cm in diameter), which may have originated from the right adrenal gland and was closely related to the liver. Transthoracic echocardiography showed a strong echogenic filling measuring 70 mm extended from the IVC into the right atrium and ventricle. After preoperative preparation with cardiopulmonary bypass, sufficient blood products, transesophageal echocardiography and multiple monitoring, tumor and thrombus...
Ewing’s sarcoma; Anesthesia; Inferior vena cava; Cardiac arrest; Tumor thrombus

INTRODUCTION

The Ewing’s sarcoma family is an aggressive group of childhood cancers, including classic Ewing’s sarcoma, Askin tumor, and peripheral primitive neuroectodermal tumor[1]. Extraosseous Ewing’s sarcoma is a rare, rapidly growing, round-cell, malignant tumor that starts anywhere in soft tissues. The average age of patients with extraosseous Ewing’s sarcoma is higher than those with bone cancer[2]. Nkx2.2 is a transcription factor that functions in neuronal and neuroendocrine differentiation, which is upregulated in Ewing’s sarcoma and required for its oncogenesis[3]. The tumor cells characteristically express CD99 (MIC2 antigen), a glycoprotein localized on cell membrane. The defining feature of Ewing’s sarcoma is a characteristic t(11;22)(q24;q12) translocation involving the Ewing’s sarcoma breakpoint region 1 (EWSR1) gene on chromosome 22 and the FLI1 gene on chromosome 11[4]. Currently, localized Ewing’s sarcoma has a relative survival rate of 75%, while the survival rate resection by IVC exploration and right atriotomy were successfully performed by a multidisciplinary team. Intraoperative hemodynamic stability was the major concern of anesthesiologists and the status of tumor thrombus and pulmonary embolism were monitored continuously. During transfer of the patient to the intensive care unit (ICU), cardiac arrest occurred without external stimulus. Cardiopulmonary resuscitation was performed immediately and cardiac function was restored after 1 min. In the ICU, extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) were provided to maintain cardiac, liver and kidney function. Histopathologic examination confirmed the diagnosis of Ewing’s sarcoma. After postoperative treatments and rehabilitation, the patient was discharged from the urology ward.

CONCLUSION

An adrenal Ewing’s sarcoma with IVC and right atrium thrombus is extremely rare, and its anesthesia and perioperative management have not been reported. Thus, this report provides significant insights in the perioperative management of patients with adrenal Ewing’s sarcoma and IVC tumor thrombus. Intraoperative circulation fluctuations and sudden cardiovascular events are the major challenges during surgery. In addition, postoperative treatments including ECMO and CRRT provide essential support in critically ill patients. Moreover, this case report also highlights the importance of multidisciplinary cooperation during treatment of the disease.

Key Words: Ewing’s sarcoma; Anesthesia; Inferior vena cava; Cardiac arrest; Tumor thrombus

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Core Tip: An adrenal Ewing’s sarcoma with IVC and right atrium thrombus is extremely rare, and its anesthesia and perioperative management have not been reported. We report tumor resection and perioperative management in a case of adrenal Ewing’s sarcoma with IVC and right atrium thrombus. After surgery, cardiac arrest occurred and CPR was successfully performed. Following postoperative treatment and rehabilitation, the patient was discharged from the hospital and then survived for more than 17 mo. Therefore, this report provides insights for the perioperative management of adrenal Ewing’s sarcoma with distant vascular extension.


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DOI: https://dx.doi.org/10.12998/wjcc.v10.i2.643

INTRODUCTION

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CASE PRESENTATION

Chief complaints
The patient presented with intermittent pain under the right costal arch for four months.

History of present illness
A 20-year old female patient presented with intermittent pain under the right costal arch for four months, and was diagnosed with an adrenal tumor with IVC and right atrium tumor thrombus. Before admission, the patient had visited a number of different hospitals. However, due to the position and size of the tumor, and complications such as pulmonary embolism, no surgery was performed. The Department of Urology in our hospital has treated more than 100 cases of adrenal or renal tumors with Mayo Clinic stage I-IV tumor thrombus[17,18]. Thus, we have experience in tumor excision and emergency treatment for these circumstances. Considering the rapid development of the tumor and risks of a stuck valve that could occur at any time, the patient was admitted to hospital. Prior to admission, the patient and her family members were fully informed that the operation was a form of palliative treatment.

History of past illness
The patient had no remarkable past medical history.

Personal and family history
The patient had no remarkable personal and family history.

Physical examination
Physical examination showed a temperature of 37 °C, heart rate (HR) of 101 bpm, blood pressure (BP) of 92/60 mmHg, respiratory rate of 17 breaths/min, and oxygen saturation (SpO2) of 91% in room air.

Laboratory examinations
Laboratory examinations showed an elevation of renin 1.51 ng/mL/h (normal range: 0.05-0.79 ng/mL/h) and angiotensin II 191.01 pg/L (normal range: 55.3-115.3 pg/L). The high renin-angiotensin secretion was possibly attributed to decreased renal perfusion. The 24 h urine catecholamine levels were normal and pheochromocytoma was excluded. Although endocrine changes were not typical, adrenal cortical carcinoma was highly suspected. Reduced platelets (PLT, 68 × 10^9/L) and an abnormal
Table 1 Summary of reported cases of Ewing’s sarcoma rising from the adrenal gland with inferior vena cava tumor thrombus

<table>
<thead>
<tr>
<th>No</th>
<th>Ref.</th>
<th>Age</th>
<th>Gender</th>
<th>Position</th>
<th>Tumor size, cm</th>
<th>Initial infiltration or metastasis</th>
<th>Surgical procedure</th>
<th>Outcome at time of report</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zhang et al[14]</td>
<td>30</td>
<td>M</td>
<td>R</td>
<td>12</td>
<td>IVC tumor thrombus</td>
<td>Adr</td>
<td>Dead (8 mo)</td>
</tr>
<tr>
<td>2</td>
<td>Zhang et al[14]</td>
<td>22</td>
<td>M</td>
<td>L</td>
<td>17</td>
<td>IVC tumor thrombus</td>
<td>Adr + Neph + Spl + IVCt</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>Abi-Raad et al [4]</td>
<td>26</td>
<td>F</td>
<td>L</td>
<td>11.3</td>
<td>IVC tumor thrombus</td>
<td>Adr + Neph + Spl + IVCt</td>
<td>Alive (8 mo)</td>
</tr>
<tr>
<td>5</td>
<td>Saboo et al[16]</td>
<td>26</td>
<td>F</td>
<td>L</td>
<td>Large</td>
<td>IVC tumor thrombus</td>
<td>No surgery</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Present case</td>
<td>20</td>
<td>F</td>
<td>R</td>
<td>22</td>
<td>Liver, IVC, RA tumor thrombus</td>
<td>Liver + Adr + IVCt + RAat</td>
<td>Alive</td>
</tr>
</tbody>
</table>

F: Female; M: Male; L: Left; R: Right; Adr: Adrenalectomy; Neph: Nephrectomy; Spl: Splenectomy; IVCt: Inferior vena cava thrombectomy; RA: Right atrium; NR: Not recorded.

Imaging examinations
Enhanced abdominal computed tomography (CT) showed a retroperitoneal mass with a diameter of 22 cm, which most likely originated from the right adrenal gland and was closely related to the liver (Figure 1). Positron emission tomography-CT (PET-CT) revealed a huge heterogeneous mass with elevated glucose metabolism in the right hepatic lobe and the space between the liver and the right kidney. Transthoracic echocardiography (TTE) showed that the proximal IVC was 25.7 mm wide with a strong echogenic filling extending into the right atrium and ventricle and the distant tumor thrombus was 70 mm approximately. Preoperative left ventricular ejection fraction (LVEF) was 64% (Figure 2A). Cardiac enhanced magnetic resonance imaging (MRI) confirmed the filling in the right atrium and ventricle (Figure 2B).

MULTIDISCIPLINARY EXPERT CONSULTATION
Five days before surgery, the patient developed a sudden shortness of breath at rest, accompanied by a sense of pressure behind the sternum and in the scapular area for one hour. During this time, her BP and HR were 105/79 mmHg and 116 bpm, respectively. Immediate arterial blood gas analysis showed: pH 7.49, PaCO$_2$ 22.5 mmHg, PaO$_2$ 58 mmHg, lactate 3 mmol/L, SpO$_2$ 94%. Electrocardiogram showed sinus tachycardia (118 bpm), inverted T waves were observed in chest leads, and visible Q waves in II, III, aVF leads, but there were no significant changes in myocardial injury markers. Cardiac MRI and pulmonary artery Computed Tomography Angiography (CTA) showed no pulmonary embolism. Her symptoms were relieved after 4 L/min oxygen therapy (nasal cannula). The cardiologist examined the patient and speculated that the tumor thrombus in the right atrium and ventricle affected tricuspid valve motion, as well as the occurrence of pulmonary embolism.

Several days later, the multidisciplinary team composed of urological surgeons, cardiac surgeons, general surgeons, anesthesiologists and ICU physicians evaluated the tumor status and cardiac function and decided to perform surgery to prevent a severe stuck valve and right heart failure. The most significant indication for a stuck valve is the “roller coaster”-like BP, accompanied by clinical symptoms such as dyspnea at rest, chest pain, low output, shock, embolization, and even cardiac arrest [19,20]. Considering that a severe stuck valve and right heart failure could occur at any time, the multidisciplinary team decided to perform tumor and thrombus resection directly, but not after preoperative biopsy.
Figure 1 Retroperitoneal mass detected on enhanced abdominal computed tomography. The yellow arrow indicates the tumor was closely related to the liver.

Figure 2 Tumor thrombus detected in the inferior vena cava and right atrium. A: Preoperative transthoracic echocardiography showed that the tumor thrombus extended into the right atrium. Red areas indicate tumor thrombus; B: Cardiac enhanced magnetic resonance imaging showed tumor thrombus in the inferior vena cava (IVC) and the right atrium. The upper yellow arrow indicates tumor thrombus in the right atrium. The lower yellow arrow indicates tumor thrombus in the IVC.

**FINAL DIAGNOSIS**

Histopathologic examination of the resected tissue showed that the tumor was surrounded by normal adrenal tissue, which suggested that the tumor originated in the adrenal gland (Figure 3A and B). Figure 3C shows tumor cells with round nuclei and pale cytoplasm, as well as their rosette structures, which confirmed the diagnosis of Ewing’s sarcoma. Immunohistochemistry revealed that the tumor cells were positive for CD99 and Nkx2.2, well-known markers for Ewing’s sarcoma (Figure 3D and E). Furthermore, fluorescence in situ hybridization studies showed rearrangement of the EWSR1 gene in the nuclei of tumor cells (Figure 3F). These results confirmed that the tumor was Ewing’s sarcoma with an adrenal origin.

**TREATMENT**

*Intraoperative treatment*

The patient underwent surgery. In the pre-operation room, 10 mg diazepam was given intravenously to relieve the patient’s anxiety, and she was then transferred to the operating room. The initial BP, HR and SpO₂ were 93/65 mmHg, 110 bpm and 90% (in room air), respectively. Two peripheral venous access points (16 G) were established, and the left radial artery was cannulated for continuous arterial blood pressure monitoring. Following the above preparation, a 10-min preoxygenation (FiO₂: 50%) was performed prior to induction. For anesthesia induction, 20 μg sufentanil, 10 mg etomidate and 6 mg cisatracurium were injected in sequence. After 2 min of positive
Figure 3 Pathological findings of the resected primary tumor. A: Image of the resected tumor and thrombus; B: Hematoxylin-Eosin staining shows that the tumor (the lower part of the image) was surrounded by normal adrenal tissue (the upper part of the image), which suggested that the tumor arose in the adrenal gland (2 × magnification); C: Hematoxylin-Eosin staining shows the tumor cells with round nuclei and pale cytoplasm, as well as their rosette structures (inside the yellow circles) (20 × magnification); D: Immunohistochemistry showed CD99 positive tumor cells (20 × magnification); E: Immunohistochemistry showed Nkx2.2 positive tumor cells (20 × magnification); F: Separation of the red signal and green signal (the right two signals) by fluorescence in situ hybridization reveals Ewing’s sarcoma breakpoint region 1 gene rearrangement in the nuclei of tumor cells, while the yellow signal (the left signal) shows the normal allele.

mask ventilation, a reinforced tracheal tube was intubated. Anesthesia induction was relatively stable without obvious variation in both BP and HR. Sufentanil at 25 μg/h, 1-2 MAC of sevoflurane and intermittent cisatracurium were used for anesthesia maintenance. The bispectral index (BIS) was maintained within 40 and 60. Right internal jugular vein puncture was performed to place the central venous catheter for central venous pressure (CVP) monitoring. The TEE probe was inserted to assist surgeons and anesthesiologists to determine the clearance of thrombus, the changes in heart function and the occurrence of pulmonary embolism.

After a series of preparations, the surgery was performed on schedule. As the tumor was closely related to the liver, laparotomy was chosen to reduce blood loss. At the beginning of surgery, an incision was made 2 cm below the right costal margin from the xiphoid to the posterior line of the axilla and was extended about 10 cm below the left costal margin. It was found that the liver was compressed to the left by the tumor. Firstly, the liver and duodenum were dissociated to expose the right kidney and IVC. Then, the dissociation between the lower pole of the tumor and the kidney was extended, and other parts of the tumor were dissociated to expose the right renal vein, right renal artery, right ureter, and to retain the right kidney. During tumor dissociation, the circulation was unstable with the lowest BP of 70/40 mmHg (Table 2). The reasons for this were as follows: (1) The tumor was closely related to the liver and the lower margin of liver bleeding was serious during the dissociation process; and (2) The tumor was huge, and its dissociation caused obstruction of the heart outflow tract by IVC thrombus resulting in decreased BP. In order to maintain BP and HR within a relatively safe range, norepinephrine (0.02-0.04 μg/kg/min) and dopamine (5-15 μg/kg/min) were continuously infused, and 1 g/h tranexamic acid was administered as an anti-fibrinolytic to reduce bleeding[21]. After careful dissociation, the tumor was successfully dissected from the kidney, liver and retroperitoneum.

The cardiac surgeon continued with a median sternotomy, and after systemic heparinization, the IVC, superior vena cava and the ascending aorta were cannulated to establish cardiopulmonary bypass. Blood gas analysis was performed hourly and parameters were modulated. Before the ascending aorta was cross-clamped, the patient was gradually cooled to 32 °C. After the infusion of cold cardioplegia into the aortic root, cardiac arrest was achieved. The right atrium was opened to reveal part of the tumor thrombus. The remaining tumor thrombus was pushed into the IVC, which was removed after blocking the proximal and distal ends of the IVC. Intraoperative TEE examination confirmed the removal of tumor thrombus in the right atrium and
ventricle. However, tough cord-like thrombus remained in the IVC closely related to the liver. Blind removal could damage the IVC and tumor fragmentation may cause pulmonary embolism[22], and satisfactory complete resection can only be achieved via liver transplantation[23,24]. Furthermore, the previous reports of renal cell carcinoma indicated that resection of the residual thrombus did not improve the prognosis[10]. After repairing the right atrium and vena cava, the patient was rewarmed and weaned off cardiopulmonary bypass. During cardiopulmonary bypass, her BP remained relatively stable. Vital signs and ventilation parameters during surgery are shown in Table 2, and arterial gas results during surgery are shown in Table 3. The resected tumor is shown in Figure 3A.

In summary, the surgical time was 587 min, intraoperative blood loss and urine were 4,500 mL and 600 mL, respectively. 14 U of red blood cells, 2200 mL of plasma, 1000 mL of colloid solution and 7200 mL of crystal solution were infused. Intraoperative complications were limited to blood loss of 500 mL from the lower margin of the liver during the dissociation and incomplete tumor and thrombus resection. Based on previous studies, blind removal may not improve the prognosis obviously in some patients[10], and the main focus of intraoperative anesthesia management was circulation maintenance and monitoring.

**Postoperative treatment**

When the patient was transferred to the ICU, the normal ECG waveform and pulse oxygen waveform suddenly disappeared, along with the carotid pulse. Cardiopulmonary resuscitation (CPR) was performed immediately, 1 mg adrenaline was injected intravenously, and the defibrillator was prepared. One minute later, the heartbeat was restored. After 5 min, the BP, HR and SpO2 were 140/100 mmHg, 120 bpm and 100%, respectively. Emergency TTE examination indicated that the chamber of ventricles was small with hypokinesis, and LVEF was 34%, but no obvious tumor thrombus was detected in the right atrium or pulmonary arteries.

After the vital signs of the patient had stabilized for 30 min, she was transferred to the ICU. On the first day, the patient developed acute liver failure (AST 7,448 U/L, ALT 3,458 U/L, ALB 24.2 g/L, TBIL 72.2 μmol/L) and renal failure (no urine with Cr 136 μmol/L). CRRT was performed, hepatoprotective agents including magnesium isoglycyrrhizinate and glutathione were used, and coagulation factors were supplemented to improve coagulation function. Cardiogenic shock and acidosis occurred after cardiac resuscitation and could not be corrected by medication. TTE indicated abnormal motion in the wall of the right ventricle and the middle and apex of the left ventricle (LVEF 38%). Therefore, ECMO was given on day two. The principle of treatment in the ICU was mainly to improve liver, kidney and heart function. During CRRT and ECMO treatment, anticoagulation was provided, which caused bleeding in the surgical area. On day twelve in the ICU, TTE showed a cord-like mass in the IVC (Figure 4), which was consistent with the intraoperative TEE result, without obvious progress. ECMO was successfully withdrawn on day twelve when the LVEF recovered (LVEF 46%) and BP was relatively stable. A total of 12 U of red blood cells, 3600 mL of plasma and 6 U of platelets were infused. On day thirteen in the ICU, the patient was conscious. The BP and HR were 99-120/50-60 mmHg and 85 bpm, respectively. TTE indicated that LVEF was 58%. The endotracheal tube was removed, and the patient was transferred to the urology ward.

In the urology ward, treatment was focused on postoperative pleural effusion and rehabilitation. Closed thoracic drainage was used for pleural effusion, and opioids and flurbiprofen were used for pain management. Eventually, the patient was discharged
Table 3 Arterial gas analysis during surgery

<table>
<thead>
<tr>
<th>Time point</th>
<th>After intubation</th>
<th>Before CPB</th>
<th>After CPB</th>
<th>Postoperative</th>
<th>After CPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.29</td>
<td>7.20</td>
<td>7.32</td>
<td>7.46</td>
<td>7.35</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>198</td>
<td>385</td>
<td>372</td>
<td>419</td>
<td>370</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>44</td>
<td>36</td>
<td>32</td>
<td>30</td>
<td>44</td>
</tr>
<tr>
<td>BE (mEq/L)</td>
<td>-5.9</td>
<td>-12.9</td>
<td>-4.5</td>
<td>-2.5</td>
<td>-1.9</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>120</td>
<td>82</td>
<td>54</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>K⁺ (mmol/L)</td>
<td>4.3</td>
<td>5.6</td>
<td>4.7</td>
<td>3.8</td>
<td>4.4</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>20.5</td>
<td>14</td>
<td>21.1</td>
<td>21.0</td>
<td>23.6</td>
</tr>
<tr>
<td>Glu (mmol/L)</td>
<td>4.7</td>
<td>8.4</td>
<td>7.8</td>
<td>7.2</td>
<td>8.7</td>
</tr>
</tbody>
</table>

CPB: Cardiopulmonary bypass; CPR: Cardiopulmonary resuscitation.

Figure 4 Echocardiogram. A: The postoperative transthoracic echocardiography examination in the intensive care unit showed that there was no obvious tumor thrombus in the right atrium; B: There was a 7 cm diameter mass in the inferior vena cava.

With improved physical status and sleep quality, and without chest pain. Cardiac function was restored to the preoperative level (LVEF 63%). Perioperative blood tests for red and white cells, hemoglobin, coagulation and inflammation (procalcitonin, PCT, a parameter to estimate the severity, prognosis, and time course of the inflammatory response) are summarized in Table 4.

OUTCOME AND FOLLOW-UP

The patient received chemotherapy after surgery. Firstly, she received three courses of Ifosfamide and Etoposide combination chemotherapy every 21 d. Considering the local recurrence of liver metastasis, she received another six courses of Gemcitabine and Taxotere combination chemotherapy every 21 d. So far, liver metastasis has reduced and the IVC tumor thrombus has not changed since surgery. The timeline of perioperative therapies and outcome are summarized in Figure 5. There was no obvious progression of the residual IVC tumor thrombus. Since discharge, the patient has survived for 20 mo, and we will continue to monitor her for some time.

DISCUSSION

Extrasosseous Ewing’s sarcoma is rare, and its overall incidence is 1% of all sarcomas [25]. To date, 39 cases of Ewing’s sarcoma arising from the adrenal gland have been reported [26-29], five of which were initially diagnosed with IVC thrombus (Table 1). The follow-up time ranged from 1 to 36 mo and the survival time was correlated with the clinical stage at diagnosis. There are two prognostic factors to predict the
Table 4 Perioperative vital laboratory data

<table>
<thead>
<tr>
<th>Time point</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Discharged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell (× 10⁹)</td>
<td>5.02</td>
<td>3.15</td>
<td>3.09</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>113</td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td>White cell count (× 10⁹)</td>
<td>5.27</td>
<td>8.02</td>
<td>2.86</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>57.7</td>
<td>84.7</td>
<td>70</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>22.7</td>
<td>11.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>---</td>
<td>1.82</td>
<td>0.126</td>
</tr>
<tr>
<td>Platelets (× 10⁹)</td>
<td>113</td>
<td>63</td>
<td>156</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>32</td>
<td>32.5</td>
<td>29.5</td>
</tr>
<tr>
<td>PT (s)</td>
<td>15.5</td>
<td>14.5</td>
<td>12.1</td>
</tr>
<tr>
<td>INR</td>
<td>1.45</td>
<td>1.36</td>
<td>1.21</td>
</tr>
<tr>
<td>Coagulation factor VIII (%)</td>
<td>---</td>
<td>94.2</td>
<td>150</td>
</tr>
<tr>
<td>D-dimer</td>
<td>---</td>
<td>8.31</td>
<td>2.78</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.8</td>
<td>1.08</td>
<td>2.9</td>
</tr>
</tbody>
</table>

PCT: Procalcitonin.

recurrence of Ewing’s sarcoma: disease-free interval (DFI) between diagnosis and first relapse and the site of recurrence. The patients with DFI > 2 years have an estimated 5-year overall survival of approximately 30%, but those with DFI < 2 years have an estimated 5-year overall survival of only 7%. In addition, patients with combined local and distant relapse have the worst outcomes, while those with isolated local recurrences appear to fare better[30].

Laparotomy combined with thoracotomy is the primary treatment and has become a major significant challenge for anesthesia and perioperative management. Furthermore, the present case was unconventional in anesthetic practice according to the adrenal Ewing’s sarcoma and its combination with IVC and right atrium thrombus, which resulted in vascular obstruction and hemodynamic disturbance. Besides, the primary tumor also directly induced abnormal hormone levels. During transfer to the ICU, the patient developed sudden cardiac arrest. Although the heartbeat was soon restored, cardiac function was still poor, requiring ECMO support. Liver and kidney dysfunction were also a problem. Appropriate treatment has led to improved prognosis, but the underlying mechanisms and therapeutic improvements are still worth exploring.

To date, published cases with tumor thrombus have focused on adrenal pheochromocytoma/renal cell carcinoma with tumor thrombus, and radical surgery with cardiopulmonary bypass and hypothermic circulatory arrest are recommended[31-33]. Extraosseous Ewing’s sarcoma has a neuroendocrine function and secretes endocrine markers including CD56, Syn and CgA[34], and could affect the cardiovascular stabilization and internal environment. Surgical resection could be the treatment for patients with Ewing’s sarcoma[35,36], while surgery and anesthetic management for patients with IVC and atrium thrombus have numerous unpredictable risks and challenges.

In this case, the tumor was approximately 22 cm in diameter, and the thrombus extended from the IVC into the right atrium and ventricle. According to the Mayo Clinic classification, the thrombus level was grade IV[33]. The key point of anesthetic management is to maintain perioperative hemodynamic stability, and multiple monitoring including EEG, IABP, CVP, temperature, respiratory parameters and blood gas analysis was employed during the perioperative period. Diazepam was given to relieve preoperative anxiety, and anesthetics with little effect on hemodynamics including etomidate, sevoflurane, sufentanil and cisatracurium were used for anesthetic induction and maintenance. Fluid management and vasoactive drugs are also important components for perioperative hemodynamic management. It has been reported that the perioperative outcomes favored goal directed therapy rather than liberal fluid therapy[37]. Considering infiltration of the tumor in the liver and possible bleeding, we performed volume preloading, and used norepinephrine and dopamine
to prevent hypotension during the process of dissociation. During and after cardiopulmonary bypass, her BP remained relatively stable, and transfusion was performed according to blood loss. The total intraoperative transfusion included 14 U of red blood cells, 3200 mL of plasma and colloid solution, and 7200 mL of crystal solution. TEE can be used for these procedures, as close monitoring is pivotal for hemodynamic maintenance[38]. Furthermore, TEE was used in the ICU to monitor heart function and residual thrombus, as well as the occurrence of pulmonary embolism.

During surgery, although the circulation fluctuated due to excessive bleeding, the circulation was controlled by a series of therapies. However, the patient experienced a sudden cardiac arrest after surgery. The multidisciplinary team considered that this was due to the following reasons: (1) According to the liver infiltration, the tumor was
not completely resected, thus, pulmonary embolism caused by residual tumor was considered as the primary cause. Although TTE did not provide definite evidence of the embolus, the chamber of the right ventricle was small with hypokinesia, which could be the result of acute pulmonary embolism; (2) During surgery, the patient lost 4,500 mL of blood and received 13,550 mL fluid and blood transfusions. The bleeding and rehydration, as well as cardiopulmonary bypass, could be an unusual burden on the heart and result in acute coronary syndrome, even cardiac arrest; and (3) Pathological examination indicated that the tumor was Ewing’s sarcoma, which can secrete a range of pro-inflammatory cytokines, and lead to perioperative septic shock [33,39,40]. In addition, the tumor excision process promoted the release of these mediators and could invoke a systemic inflammatory response (SIRS) and shock. Perioperative vital laboratory data are shown in Table 4. The level of PCT (1.82 ng/mL) and the percentage of neutrophils (84.7%) increased after surgery. PCT has been reported to be a better parameter for estimating the severity, prognosis, and time course of SIRS, than CRP[41]. These results indicated possible postoperative SIRS in the present case.

CONCLUSION

In conclusion, giant adrenal Ewing’s sarcoma with IVC and right atrium thrombus is a rare and challenging scenario. In the present case, a comprehensive evaluation of tumor thrombus extension was performed preoperatively. For tumor resection with excessive bleeding, adequate blood product preparation, proper selection of anesthetics and vasoactive agents, as well as intraoperative monitoring including TEE, BP, CVP, airway pressure and blood gas analysis are equally important. Perioperative compromised cardiac function and circulation fluctuations, as well as pulmonary embolism and acute cardiovascular event, are the major difficulties in anesthetic management.

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Full-endoscopic spine surgery treatment of lumbar foraminal stenosis after osteoporotic vertebral compression fractures: A case report

Quan-Lai Zhao, Kun-Peng Hou, Zhong-Xuan Wu, Liang Xiao, Hong-Guang Xu

ORCID number: Quan-Lai Zhao 0000-0002-9978-4858, Kun-Peng Hou 0000-0002-2881-7405, Zhong-Xuan Wu 0000-0003-2733-8231, Liang Xiao 0000-0002-5779-6092, Hong-Guang Xu 0000-0001-5231-3779.

Author contributions: Zhao QL and Wu ZX performed the full-endoscopic spine surgery and applied the continuous treatment; Xu HG and Xiao L validated the data and visualization; Hou KP searched the literature; Zhao QL drafted the manuscript.

Informed consent statement: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Country/Territory of origin: China

CASE REPORT

Full-endoscopic spine surgery treatment of lumbar foraminal stenosis after osteoporotic vertebral compression fractures: A case report

Quan-Lai Zhao, Kun-Peng Hou, Zhong-Xuan Wu, Liang Xiao, Hong-Guang Xu, Department of Spine Surgery, Wannan Medical College, Wuhu 241001, Anhui Province, China

Corresponding author: Hong-Guang Xu, PhD, Professor, Department of Spine Surgery, Wannan Medical College, No. 2 Zheshan West Road, Wuhu 241001, Anhui Province, China. pumchxuhg@126.com

Abstract

BACKGROUND
Few reports have described lumbar foraminal stenosis-induced radiculopathy after treatment by full-endoscopic spine surgery (FESS) combined with percutaneous vertebroplasty (PVP) in patients with vertebral compression fractures. We herein report such a case, including the patient’s treatment process and doctor’s surgical experience.

CASE SUMMARY
A 79-year-old man presented with symptoms of radiculopathy after sustaining L4 vertebral compression fractures. Imaging and physical examination revealed L4 vertebral compression fractures combined with L3/4 Lumbar foraminal stenosis (LFS). The patient’s symptoms were low back pain with pain in the lateral left leg. Although many reports have described radiculopathy induced by osteoporotic vertebroplasty fractures, the use of FESS combined with PVP has rarely been reported. This case report indicates that the combination of FESS and PVP is a safe and effective approach for the treatment of LFS-induced radiculopathy after vertebral compression fractures. This minimally invasive technique has great potential to replace traditional lumbar fixation and decompression surgery. Thus, we suggest the continued accumulation of similar cases to discuss the wider application of FESS.

CONCLUSION
For patients with osteoporotic vertebral compression fracture (OVCF) and LFS, PVP and FESS can be used to restore the vertebral height and reduce the pressure around the intervertebral foramen. Additionally, the combination of FESS and PVP can treat the pain or numbness of the low back and lower limbs and allow for recovery in a short time with excellent postoperative effects. In general, FESS is a good treatment for radiculopathy caused by foraminal stenosis after OVCF.
INTRODUCTION

Osteoporotic vertebral compression fracture (OVCF) is the most common spinal fracture in elderly people[1] and is caused by osteoporosis, violent trauma, or spinal tumours. Traditional percutaneous vertebroplasty (PVP) under X-ray fluoroscopy is a safe and effective surgical approach for the treatment of OVCFs in elderly patients[2]. Lumbar foraminal stenosis (LFS) is one of the more serious lumbar degenerative diseases among patients with low back and leg pain, leading to nerve root compression in corresponding lumbar segments[3]. LFS can be aggravated by spinal degeneration, which is characterized by aggravation of symptoms during lumbar extension. Full-endoscopic spine surgery (FESS) has become one of the main approaches of minimally invasive spinal surgery for lumbar intervertebral disc degeneration. Because of the rapid development of visualization technology in the field of spinal endoscopy, the application range of spinal endoscopy to treat spinal degenerative diseases has shifted from simple disc protrusion to spinal canal stenosis, including central canal stenosis and nerve root canal stenosis[4]. The surgical technique of enlarging the intervertebral foramen area by facet arthroplasty to treat root canal stenosis and decompression of the nerve root has been well developed[5]. FESS has been widely used by spine surgeons, but there are few reports about the combination of PVP with FESS in the treatment of concurrent OVCF and LFS. We herein report a rare case of lumbar vertebral compression fracture after osteoporotic vertebral compression fractures: A case report. World J Clin Cases 2022; 10(2): 656-662

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i2.656

CASE PRESENTATION

Chief complaints

A 79-year-old man presented to the emergency department with a chief complaint of low back pain and limited mobility caused by an accidental fall 9 d previously.

History of present illness

The patient accidentally fell 9 d ago and failed to effectively respond to conservative treatment.

History of past illness

The patient had a history of hypertension for which he has been taking Betaloc tablets over an extended period of time. The patient had no family history of congenital, allergic, or systemic disease.
Personal and family history
The patient had no history of familial genetic diseases.

Physical examination
Physical examination revealed a slight alteration in the physiological curvature of the spine, slight scoliosis, restricted range of motion in the lower back, tenderness over the L4 spinous process, and positive paravertebral muscle tenderness. The skin sensation of both upper extremities was normal, with a grade of 5 for muscle strength of the main muscle groups. The skin sensation of the lateral left leg was decreased, with normal sensation of the skin of the opposite leg. Straight-left leg-raise was positive above 45°. The patellar reflex of the left lower extremity was decreased, the quadriceps muscle strength of the left lower extremity was grade 4, and the right lower extremity was normal.

Laboratory examinations
Laboratory examinations, including liver function tests, renal function tests, and routine urine tests, revealed no abnormalities. Lymphocyte count, eosinophil count and haematocrit decreased slightly; neutrophils, mean corpuscular volume and D-D slightly increased; other tests such as routine whole blood and coagulation function tests were normal.

Imaging examinations
Radiography and computed tomography (CT) of the lumbar spine (Figure 1A-D) revealed an L4 vertebral compression fracture. Magnetic resonance imaging (MRI) (Figure 1E-H) showed that the left nerve root canal was significantly narrowed due to the oppression of the fracture fragment at the posterior upper edge of the L4 vertebral body (orange arrow).

FINAL DIAGNOSIS
L4 vertebral compression fracture and L3/4 Lumbar foraminal stenosis.

TREATMENT
In the first surgery, the patient underwent left L4 pedicle puncture under local anaesthesia and overall monitoring in the prone position. During close monitoring of the patient’s vital signs, approximately 3.3 mL of bone cement was injected into the L4 vertebral body through the unilateral pedicle. Postoperatively, the mobility of the lower extremities recovered to baseline. Low back pain was significantly relieved, but left lateral leg pain was still present. The patient was instructed to take an oral form of diclofenac sodium sustained-release tablets, eperisone, and a neurotrophic drug. One week later, the pain was still present. Postoperative lumbar anteroposterior and lateral X-rays (Figure 2A and B), lumbar CT (Figure 2C), and lumbar MRI (Figure 2D and E) revealed changes in the L4 vertebral body after bone cement injection, particularly bone marrow oedema of the L4 vertebral body, as well as bilateral thickening of the ligamentum flavum at the L3/4 level. After PVP, necrosis was still present in the lateral recess of the L3/4 intervertebral foramen (orange arrow).

The patient then underwent FESS under local anaesthesia and decompression of the root canal of the L3/4 left nerve. Intraoperatively, significant hyperplasia of the L3/4 left articular process and hypertrophy of the ligamentum flavum were observed. The hypertrophic ligamentum flavum was removed, and the nerve root was fully released. The surgery was successful. Postoperatively, the patient underwent electrocardiographic monitoring, antibiotic prophylaxis, rehydration, and symptomatic treatment with close observation of his clinical status.

OUTCOME AND FOLLOW-UP
One month after discharge, three-dimensional lumbar CT revealed postoperative changes at the site of L4 vertebral bone cement injection as well as complete decompression in the L3/4 left nerve root canal and lateral recess (Figure 3, orange arrow).
Figure 1 Imaging examination before percutaneous vertebroplasty. A: Anteroposterior X-ray before percutaneous vertebroplasty (PVP); B: Lateral X-ray before PVP; C: Sagittal computed tomography (CT) reconstruction before PVP; D: CT cross-section reconstruction before PVP; E: T1 magnetic resonance imaging (MRI) before PVP; F: T2 MRI before PVP; G: T2 fat suppression MRI before PVP; H: T2 cross section MRI before PVP.

arrow). In addition, the patient complained of occasional slight pain in the left lateral leg, possibly caused by the loss of structural support of the surrounding tissue of the L4 nerve root after decompression and contact with the bone or tissue at the decompression site with movement. At the follow-up 3 mo after discharge, the mild leg pain had completely resolved.

DISCUSSION

With the recent ageing of the global population, the incidence of vertebral compression
fractures is increasing. In a few cases, vertebral compression fractures lead to compression of the spinal cord. In addition to severe back pain, such patients develop lower extremity pain or numbness. Sasaki et al. described 66 patients with vertebral compression fractures, 10 (15.2%) of whom had persistent radiculopathy. Seven patients were diagnosed with spinal canal stenosis, two with LFS, and one with
lumbar disc herniation. Radiculopathy induced by lumbar vertebral compression fractures has been reported[8,9] and occurs secondary to LFS caused by compression of nerves by bone fragments or vertebral compression. The development of LFS after vertebral compression fractures may be due to changes in the foraminal geometry after fracture[10]. PVP and FESS may be effective approaches to relieve low back pain in patients with OVCFs combined with LFS.

We have herein reported a case of OVCF combined with LFS after lumbar fractures because of continuous movement and designed a novel endoscopic surgery technique. After PVP, FESS was performed to treat the nerve root disease induced by LFS after lumbar vertebral compression fracture, with a very satisfactory curative effect. Degenerative changes in L3/4 were observed intraoperatively, including hypertrophy of the ligamentum flavum, disc herniation, and entry of fibrous membrane-covered posterior wall debris into the intervertebral foramen. After L4 vertebral compression, the patient did not comply with the doctor’s advice regarding bed rest and instead continued his daily activities, further compressing and aggravating the L4 vertebral upper endplate, which resulted in symptoms of the lower extremity root. Severe leg pain induced by LFS after OVCF requires surgical treatment, but conservative treatment is also feasible for some patients with mild symptoms. We observed the patient for 1 wk after PVP to evaluate whether foraminal decompression could be avoided. It is possible to recover the height of the intervertebral foramen after distraction of the compressed vertebral body with bone cement. The patient’s lower extremity pain was not relieved over time under conservative treatment; therefore, FESS was performed. Weber et al[11] reported a case of radiculopathy after vertebral compression fracture in which a bone block compressed the spinal cord. After 2 wk of conservative treatment, the patient’s symptoms remained unchanged. Lumbar fusion and internal fixation were then performed, and the patient recovered well in the later stage. Isogai et al[12] reported that lumbar fusion and internal fixation were effective for radiculopathy after vertebral compression fracture. However, internal fixation is not suitable for the physical condition of elderly patients with osteoporosis. The risks of loosening of the internal fixation device and adverse reactions caused by the invasive operation are higher in these patients[13]. Our report shows that the combined use of bone cement and spinal endoscopy helps patients undergo a safer operation and achieve early rehabilitation. However, longer follow-up is required to assess the development of spinal instability over time.

Few studies to date have focused on the use of FESS in the treatment of nerve root disease induced by LFS after vertebral compression fracture. Full-visualization laminectomy or foraminal enlargement is a basic procedure of FESS. In the past, FESS was often used for lumbar discectomy[14]. In recent years, it has been gradually used for decompression of the spinal canal or nerve root canal[15], avoiding excessive medical treatment caused by unnecessary lumbar interbody fusion. Kim et al[16] reported radiculopathy caused by compression of nerve roots by osteophytes of fractured vertebrae after vertebral compression fractures. The incidence of radiculopathy in lower lumbar vertebral fractures is higher. Bone fragments (osteophytes) of the collapsed vertebrae might fall into the intervertebral foramen and directly compress the nerve roots. Philips et al[8] described three women with an average age of 81.7 years. The symptoms of nerve root compression were relieved by FESS via removal of bone cement leakage and osteophytes. Postoperative recovery was good, and no complications were observed. In this case, FESS showed good minimally invasive performance. Under spinal endoscopy, the osteophyte compressing the nerve root was completely removed, and the compressed part of the intervertebral foramen was relieved, thus avoiding the tissue damage caused by lumbar open surgery.

CONCLUSION

For patients with OVCF and LFS, PVP for restoring vertebral height and FESS for decompression around the foramina can remit pain or numbness in the lower back and lower extremities, allowing the patient to recover in a short time with an excellent postoperative effect. Generally, FESS is a good treatment for LFS-induced radiculopathy after OVCF.
REFERENCES


Ethambutol-induced optic neuropathy with rare bilateral asymmetry onset: A case report

Wen-Yan Sheng, Shuang-Qing Wu, Ling-Ya Su, Li-Wei Zhu

Abstract

BACKGROUND
Ethambutol-induced optic neuropathy (EON) most commonly manifests as bilateral symmetrical loss of vision and often cause serious and irreversible visual impairment because of the lack of early detection and effective treatment. We followed a case of EON with rare binocular asymmetric clinical manifestations and observed the changes of visual function and retinal structure after drug withdrawal, so as to further understand the clinical characteristics of this disease.

CASE SUMMARY
A 54-year-old man complained of gradual visual decline in the left eye. The patient presented with best-corrected visual acuity of 20/20 in the right eye and 20/50 in the left eye. Color vision examination revealed difficulty in reading green color plates in the left eye. The visual field manifested as concentric contraction in the left eye. After nearly a month of drug withdrawal, the right eye had a similar decline in visual function. At the last visit, 19 mo after drug withdrawal, the visual function significantly recovered in both eyes. During follow-up optical coherence tomography (OCT) examination, both eyes manifested the thickness of the retinal nerve fiber layer from mild thickening to thinning and finally temporal atrophy, and the ganglion cell-inner plexiform layer showed significant thinning. The difference was that a reversible structural disorder in the outer retina of the nasal macula was detected in the left eye by macular high-definition OCT.

CONCLUSION
Nephropathy and high blood pressure, which damage the retinal microcirculation, may cause damage to the outer layer of the retina. Ethambutol may influence photoreceptor as well as retinal ganglion cells.

Key Words: Ethambutol-induced optic neuropathy; Retinal nerve fiber layer; Ganglion
A 54-year-old male patient was admitted to the Department of Ophthalmology of Affiliated Hangzhou Chest Hospital, Zhejiang University School of Medicine (Hangzhou, Zhejiang Province, China), on September 1, 2019. The patient complained of gradual painless loss of vision in the left eye for 5 mo.

History of present illness
The patient had been diagnosed with tuberculosis of thoracic vertebrae 10 mo earlier in the Tuberculosis Department. Because this patient suffered from renal failure, the tuberculologist did not use an intensive treatment plan. He received daily combination treatment consisting of 750 mg ethambutol (11.5 mg/kg), 600 mg rifampin, and 300 mg isoniazid. After 2 wk, the patient had an allergic rash and drug-induced liver damage, so rifampin was discontinued. Therefore, the patient was finally treated with ethambutol and isoniazid for 10 mo, until loss of vision developed and he came to the ophthalmology clinic.

History of past illness
The patient had a history of renal dysfunction and renal hypertension (blood pressure 160/98 mmHg) for about 10 years, and he had been undergoing abdominal dialysis treatment for up to 8 years. He had no history of diabetes or any other eye diseases. The patient complained that he could correctly judge the traffic lights before the onset of the disease and denied a history of color vision dysfunction.

Personal and family history
The patient was married and had a son. His grandparents, parents and son did not have a history of color vision dysfunction.

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have similar episodes of loss of vision. He denied smoking and alcohol consumption.

**Physical examination**
At the first visit, the best-corrected visual acuity was 20/20 in the right eye and 20/50 in the left eye. Color vision examination with Ishihara color plates revealed a difficulty in reading green color plates in the left eye. Pupillary reactions were normal with no relative afferent pupillary defect. Intraocular pressure was 15 and 14 mmHg with applanation tonometry. Slit-lamp microscopy of the bilateral anterior segments did not reveal any abnormality. Fundus examination showed normal appearance of the disk in both eyes (Figure 1). The Humphrey Field Analyzer (with SITA-FAST strategy and C30-2 program; Carl Zeiss Meditec, Dublin, CA, USA) was used for visual field examination. Concentric contraction was observed in the left eye, and there was no obvious visual field defect in the right eye (Figure 2).

**Laboratory examinations**
The renal function was abnormal: urea nitrogen 26.51 mmol/L (normal range 3.1-8.8 mmol/L), creatinine 1123.9 μmol/L (normal range 44-133 μmol/L), uric acid 359 mmol/L (normal range 90-420 mmol/L).

**Imaging examinations**
Cranial and orbit magnetic resonance examinations did not show any abnormal lesions. Cirrus high-definition optical coherence tomography (OCT) (Carl Zeiss Meditec) examination showed that, in the left eye, the peripapillary retinal nerve fiber layer (p-RNFL) slightly increased on the temporal side (Figure 3), and the thickness of the ganglion cell layer and inner plexiform layer (GCIPL) decreased (Figure 4). In the right eye, GCIPL was normal, but the thickness of p-RNFL increased on the inferior, superior and temporal sides. We found that the outer nuclear layer under the fovea and outer reflection bands representing the photoreceptor cells of the left eye were blurred (mainly the ellipsoid zone and intersection area), and the damaged intersection area was mainly on the nasal side of the macula (Figure 5).

**FINAL DIAGNOSIS**
EON, based on ocular examination and clinical findings.

**TREATMENT**
Treatment with ethambutol and isoniazid was immediately discontinued, and the patient received oral administration of vitamin B12, vitamin C, and mecobalamin for 6 mo.

**OUTCOME AND FOLLOW-UP**
At nearly 1 mo after discontinuation of ethambutol, the visual function in both eyes had deteriorated further. The best-corrected visual acuity was 20/200 in the left eye and 20/200 in the right eye. The color vision test revealed that both red and green were indistinguishable in the left and right eyes. At the third visit, 6 mo after discontinuation of ethambutol, the best-corrected visual acuity was 20/80 in the right eye and 20/200 in the left eye. Color vision examination remained red and green dyschromatopsia in both eyes. At the fourth visit, 19 mo after discontinuation of ethambutol, the best-corrected visual acuity improved to 20/20 in the right eye and 20/50 in the left eye. Color vision examination also showed recovery; only some pictures with green color were indistinguishable in both eyes.

**DISCUSSION**
The exact pathophysiological mechanism underlying EON is still unclear, although it may be caused by disrupted oxidative phosphorylation secondary to decreased available copper in the human mitochondria, or from inhibited lysosomal activation.
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Figure 1 Color fundus photography at the initial visit. The optic disk of both eyes was normal at the initial visit.

Figure 2 Computer perimetry results of four follow-up visits. A: At the initial visit, there were suspicious dark spots in the inferonasal region of the right eye, and the visual field defect of the left eye manifested as concentric contraction; B: At the second visit, visual field defects had worsened in the right eye; C: At the third visit, the defect showed progression in the left eye, but improved in the right eye; D: At the fourth visit, the visual field in both eyes improved.

due to zinc chelation[4]. There have been studies stating that EON is a dose- and time-dependent adverse effect[5]. The frequency of visual impairment has been reported in 50% of patients at a dose of 60-100 mg/kg/d, 5%-6% at 25 mg/kg/d, and 1% at 15 mg/kg/d. Visual loss is typically insidious and symmetrical, occurring typically 2-8 mo after initiation of therapy[6]. However, a controlled study of 231 patients found that age > 65 years, hypertension, and kidney disease were also risk factors for the development of EON[2,7].

In > 60% of patients with EON, ocular examination reveals bilateral, painless and typically symmetric loss of visual acuity and abnormal color vision[8]. However, the onset may be unilateral, but eventually both eyes are involved[1]. Loss of color vision is typically reported for green and red, although blue-yellow color changes may also occur[9,10]. Initially, the optic disc may appear normal; however, as the disease progresses, it eventually develops into a pale optic disc[11,12]. Visual field test usually reveals central or paracentral scotoma and less commonly includes peripheral constriction, altitudinal field defects, and bilateral temporal field defects[13]. The diagnosis of EON is based on the identification of a toxic factor and exclusion of other pathologies exhibiting a similar clinical profile. Differential diagnoses include Leber’s hereditary optic neuropathy, dominantly inherited optic neuropathy, compressive or infiltrative lesion of optic chiasm, bilateral inflammatory or demyelinating optic neuropathy, maculopathies/macular dystrophy. Often, visual loss from EON can be regained after stopping the drug. The amount and time frame for visual recovery varies. If detected early and with prompt discontinuation of ethambutol, between 30% and 64% of patients show some improvement in their visual disturbances over a period of several months. However, even in patients who report improvement after
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Sheng WY et al. Therapy discontinuation, complete recovery is not always achieved[14]. Progressive worsening of vision after ethambutol discontinuation has also been documented[15].

In this report, the patient was referred to the ophthalmology department after 10 mo of antituberculosis therapy with a gradual painless loss of vision in the left eye for 5 mo. At the first visit, color visual dysfunction and visual field defects were detected only in the left eye. OCT examinations showed that the RNFL had a slight thickening and the thickness of GCIPL became thinner. Magnetic resonance imaging of the head and orbital optic nerves was normal. Although the present patient could not be checked for any mitochondrial DNA mutations, but combined with the patient’s medication history and clinical manifestations, we diagnosed EON. Although the patient was within the safe dose range, toxic optic neuropathy occurred and was attributed to renal dysfunction.

In the reported case, the eyes were asymmetric. The left eye had visual impairment 6 mo earlier than the right eye. At the second visit after nearly a month, the right eye showed the same visual dysfunction with a normal appearance of the optic disc. OCT examination of the right eye showed thinning of the GCIPL and mild thickening of the RNFL. The difference was that the macular high-definition scan of the left eye revealed structural damage to the outer nuclear layer, ellipsoid zone, and interdigitation zone mainly on the nasal side of the macula. After treatment, the macular lesions gradually disappeared, but there was no similar change in the right eye throughout follow-up.

OCT measurement of the RNFL are effective tools for the evaluation of optic neuropathies. Reports on the thickness of RNFL in EON are inconsistent[16-19]. These discrepancies may be attributed to different stages of the disease in the examined patients. Several studies have reported that the GCIPL was significantly thinner in patients with EON and suggested that, whether the p-RNFL was swollen or atrophic, loss of ganglion cells in the macular region had occurred[20-22]. As reported, retinal ganglion cells located in the papillomacular bundle have narrow caliber axons, rendering them even more susceptible to mitochondrial dysfunction, and contribute to RNFL atrophy on the temporal side and thinning of the GCIPL[20]. The RNFL and GCIPL changes in this patient were consistent with these reports.

Figure 3 Retinal nerve fiber layer high-definition optical coherence tomography. A: At the first visit, the retinal nerve fiber layer (RNFL) of the right eye had mild thickening in the superior, inferior and nasal regions; the RNFL of the left eye had mild thickening on the temporal side; B: Six months after drug withdrawal, the RNFL of both eyes became thinner compared with the first visit; the RNFL of the right eye was within the normal range; and the average and inferior thicknesses of the RNFL in the left eye were lower than normal; C: Eighteen months after stopping drug treatment, the RNFL of both eyes further decreased, and the temporal side of both eyes became thinner significantly.
Figure 4 Outer nuclear layer high-definition optical coherence tomography. A: At the initial visit, the outer nuclear layer under the fovea and the outer reflection bands representing the photoreceptor cells of the left eye were blurred (mainly the ellipsoid zone and the intersection area), and the damaged intersection area was mainly on the nasal side of the macula; B: Six months after drug withdrawal, compared with the first visit, the structure of the outer nuclear layer and ellipsoid zone of the macula had partially recovered; C: Eighteen months after drug withdrawal, the structure of the outer nuclear layer and the ellipsoid zone of the macula had recovered to normal appearance.

Figure 5 Ganglion cell layer and inner plexiform layer high-definition optical coherence tomography. A: At the first visit, the thickness of ganglion cell layer and inner plexiform layer (GC IPL) in the right eye was normal, and the GC IPL in the left eye was significantly lower than normal; B: At the second visit, the GC IPL of the right eye also decreased; C: At the third visit, the binocular visual function recovered, but the GC IPL was still lower than normal without any obvious recovery.

The ellipsoid zone is composed of the inner section of the photoreceptors. The interdigitation zone is the chimera between the tip of the outer section of the photoreceptor and the microvilli on the top of the retinal pigment epithelial cells. Therefore, the macular lesion in the left eye of this patient was located in the outer layer of the macula, especially the photoreceptor layer. There is a rare disease named acute macular neuro-retinopathy (AMNR) that has similar structural manifestations on OCT examination. AMNR is a rare unilateral or bilateral macular disorder. OCT images showed focal abnormalities in the photoreceptor outer segments. The pathogenesis of the disease is still unclear. The main related factors reported so far include oral contraceptives, viral infections, adrenergic receptor agonists, trauma, and chronic kidney disease[23,24]. However, this patient does not completely rule out the presence of AMNR-like lesions in the left eye, but AMNR typically occurs in young women.
presenting with sudden onset of central scotomas[25]. They correspond to sharp reddish-brown areas in the macular region. These were inconsistent with the characteristics of our case.

Ethambutol poisoning causes mitochondrial dysfunction. Although the literature describes ethambutol toxicity mainly as a neuropathy, histopathological and electrophysiological evidence supports the involvement of different retinal cell layers[26]. In this regard, we consider that he had nephropathy and high blood pressure, which damaged the retinal microcirculation, resulting in insufficient blood supply to the outer layer of the retina, and damage to the outer layer of the retina. The damage to the macula may be an important factor influencing the recovery.

After withdrawal of ethambutol for as long as 19 mo, the visual function partly recovered. The thickness of the GCIPL and RNFL on the temporal side was apparently lower than normal. A previous study also reported that, even if a patient with EON can regain 1.0 visual acuity, their visual function may not recover completely[27]. Improvement in visual acuity as the nerve fiber layer progressively thinned suggests that, while some axons had irreversible damage and underwent apoptosis, the function of the remaining axons improved as the toxic effect of ethambutol waned. Presumably some axons, including those in the papillomacular bundle, did not reach a threshold for apoptosis and were able to survive and partly recover function.

There is currently no effective treatment for EON. Drug discontinuation is the only effective management that can halt the progression of visual loss and allow recovery of vision. Some authors recommend treating patients with 100-250 mg oral zinc sulfate three times per day. If vision does not improve at 10-15 wk after stopping ethambutol, parenteral administration of 40 mg/d hydroxycobalamine (vitamin B12) for 1-28 wk has been suggested[26].

CONCLUSION
EON can occur even in cases of low-dose ethambutol administration in patients with renal dysfunction. EON is most commonly characterized by bilateral symmetrical loss of vision but may also occur successively. This report highlights the need for identification of patients at risk, adjusting the dose regimen for impaired renal function, regular monitoring for early signs of ocular toxicity, and patient education.

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Vitrectomy with residual internal limiting membrane covering and autologous blood for a secondary macular hole: A case report

Huang-Fang Ying, Shuang-Qing Wu, Wei-Ping Hu, Li-Yang Ni, Zi-Long Zhang, Yong-Gen Xu

ORCID number: Huang-Fang Ying 0000-0001-6248-3843; Shuang-Qing Wu 0000-0002-6766-4106; Wei-Ping Hu 0000-0003-1717-8262; Li-Yang Ni 0000-0001-5367-1674; Zi-Long Zhang 0000-0002-4088-9532; Yong-Gen Xu 0000-0002-9411-4759.

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BACKGROUND

Myopic foveoschisis (MF) is a common complication of pathological myopia. A macular hole (MH) usually results from the natural progression of MF and is a common complication of vitrectomy. Vitrectomy combined with residual internal limiting membrane (ILM) covering and autologous blood was effective for closing a secondary MH.

CASE SUMMARY

A 52-year-old woman presented to our clinic with a complaint of blurred vision in the right eye for 7 years. Her best corrected visual acuity (BCVA) was 20/100, axial length was 25.79 mm and standard equivalent refractive error was -10.5 dioptres. Preoperative optical coherence tomography revealed foveoschisis in the right eye. Vitrectomy with fovea-sparing ILM peeling was performed. An MH developed and gradually expanded 5 mo after the initial vitrectomy. Vitrectomy with residual ILM covering and autologous blood was performed. The MH closed 3 wk after the second vitrectomy.

CONCLUSION

Fovea-sparing ILM peeling can provide residual ILM for the treatment of MH secondary to vitrectomy for MF. Vitrectomy combined with residual ILM covering and autologous blood is effective for closing secondary MH and improving BCVA.

Key Words: Vitrectomy; Internal limiting membrane; Autologous blood; Macular hole; Myopic foveoschisis; Case report
A macular hole (MH) is a common complication after vitrectomy for myopic foveoschisis (MF). This report describes a case of an MH secondary to vitrectomy with fovea-sparing internal limiting membrane (ILM) peeling for MF. We found that the repair process of MF may be centripetal, gradually moving from the peripheral retina to the macula. Second vitrectomy with residual ILM covering and autologous blood is effective for closing secondary MH and improving best corrected visual acuity.

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INTRODUCTION

Myopic foveoschisis (MF) is a common complication of pathological myopia and is characterised by intraretinal splitting in the macular region, which can eventually develop into macular hole (MH) or even retinal detachment\cite{1,2}. It can result from the combined action of tangential and longitudinal vitreoretinal tractions, and surgery can release these two types of traction\cite{3}.

Vitrectomy is the mainstay of treatment for MF, but it is still disputable whether internal limiting membrane (ILM) peeling should be performed\cite{4}. A recent meta-analysis concluded that vitrectomy with ILM peeling may lead to a better anatomic outcome of MF than that without peeling. However, vitrectomy with ILM peeling did not significantly improve the best corrected visual acuity (BCVA) or lead to fewer complications\cite{5}. Qi et al\cite{6} reported that vitrectomy with fovea-sparing ILM peeling may lead to a better anatomic outcome of MF and fewer complications and similar visual function than that without peeling. A meta-analysis by Azuma et al\cite{3} suggested that vitrectomy with fovea-sparing ILM peeling could achieve similar anatomic outcomes in the treatment of MF, with greater visual benefits and a lower risk of MH than complete ILM peeling. Furthermore, Lai et al\cite{7} reported that vitrectomy combined with ILM repositioning and autologous blood clot was significantly effective for closing MHs, reattaching the retina and improving BCVA in patients with MH retinal detachment.

In the present case, we found that fovea-sparing ILM peeling was advantageous for providing residual ILM to treat MH secondary to vitrectomy for MF. Vitrectomy combined with residual ILM covering and autologous blood was effective for closing secondary MH and improving BCVA.

CASE PRESENTATION

Chief complaints
A 52-year-old woman presented to our hospital with a complaint of blurred vision in the right eye for 7 years.

History of present illness
The patient had no other positive symptoms.

History of past illness
The patient had no previous medical history.

Personal and family history
The patient was married and had a son. There was no family history of ocular disease.
Physical examination
At the initial examination, her BCVA was 20/100 in the right eye and 20/60 in the left eye. The standard equivalent refractive error was -10.5 dioptres in the right eye and -12.5 dioptres in the left eye. The intraocular pressures were 12.2 and 12.3 mmHg and axial lengths were 25.79 and 27.1 mm in the right and left eyes, respectively. In both eyes, the crystalline lens demonstrated opacification, and the anterior chamber was deep and clear, with tessellated fundus.

Laboratory examinations
Her prothrombin time and blood analysis, blood chemistry and urinalysis results were normal. The electrocardiographic findings were normal, and chest computed tomography showed pulmonary nodules.

Imaging examinations
Preoperative optical coherence tomography (OCT) (Figure 1A) showed that vitreo-macular traction was present in the right eye, the retinal nerve fibre layer was split on the temporal side and the outer nuclear layer was split extensively on the entire macula. Preoperative optomap (Figure 1B) revealed tessellated fundus in the right eye.

FINAL DIAGNOSIS
The final diagnosis of the case was binocular cataract, binocular MF, binocular high myopia and pulmonary nodules.

TREATMENT
Initial vitrectomy with fovea-sparing ILM peeling for MF was performed on 10 September 2020. Standard 25-G three-port pars plana vitrectomy combined with phacoemulsification and intraocular lens implantation was performed in the right eye under retrobulbar anaesthesia. After cataract surgery, the central vitreous core was removed, and the posterior hyaloid membrane was removed from the macular surface. The ILM was stained with indocyanine green (0.5 mg/mL). The ILM was removed in the macular area (fovea-sparing, 2 PD). Fluid–gas exchange was conducted with gas tamponade by room air at the end of the surgery. The patient was instructed to remain in the prone position for 3 d and avoid the supine position during the follow-up period until the gas was absorbed.

The secondary MH was detected after 1 wk, and second vitrectomy combined with residual ILM covering and autologous blood was performed 5 mo after the first surgery. Standard 25-G three-port pars plana vitrectomy was performed in the right eye under retrobulbar anaesthesia. The residual vitreous was removed, and the residual ILM was stained with indocyanine green (0.5 mg/mL). The residual ILM flap was inverted and covered the MH. Fluid–gas exchange was conducted. Then, fresh blood obtained from the patient’s vein was injected gently to cover the macula. The patient was instructed to remain in the supine position for 30 min and then change to the prone position for 3 d and avoid the supine position thereafter until the gas was absorbed.

OUTCOME AND FOLLOW-UP
Five months after the initial vitrectomy, postoperative OCT (Figure 2) demonstrated that the split range of the outer nuclear layer gradually reduced, a new split of the inner nuclear layer appeared, and the MH gradually expanded. The MH diameter was 406 μm at 1 wk after the initial vitrectomy and expanded to 617 μm at 5 mo after the initial vitrectomy. The epiretinal membrane prolifed on the residual ILM, wrinkled and caused the disordered shape of the nasal retinal nerve fibre layer.

Postoperative OCT 3 wk after the second vitrectomy revealed that the MH closed, covered by flocculent ILM (Figure 3A). The split of each layer was significantly reduced, and photoreceptor cells were absent in the macular area. Optomap (Figure 3B) revealed tessellated fundus only. The patient’s BCVA was 25/100 in the right eye, but she complained of central scotoma.
**Figure 1** Preoperative manifestation of the eye. A: Preoperative optical coherence tomography: Vitreomacular traction was observed in the right eye; the retinal nerve fibre layer was split on the temporal side, and the outer nuclear layer was split extensively on the entire macula; B: Preoperative optomap: Tessellated fundus only was observed.

**Figure 2** Changes of optical coherence tomography in the macular hole after initial vitrectomy. A: One week postoperative; B: Three weeks postoperative; C: Two months postoperative; D: Five months postoperative. Five months after the initial vitrectomy, split range of the outer nuclear layer gradually reduced, a new split of the inner nuclear layer appeared, and the macular hole gradually expanded. The epiretinal membrane proliferated on the residual internal limiting membrane, wrinkled and caused the disordered shape of the nasal retinal nerve fibre layer.

**DISCUSSION**

A recent meta-analysis reported that compared with complete ILM peeling, fovea-sparing ILM peeling may lead to similar morphological effects and may contribute to greater visual benefits and a lower risk of postoperative MH formation[3]. Fovea-sparing ILM peeling could release tangential traction force and preserve the integrity of Müller cells in the macular fovea. Thus, the traction force over the extremely thinned foveal tissue can be minimised, and less irritation and injury are helpful to maintain the stability of the macular area and avoid postoperative MH formation.

The residual ILM may contract 2-10 mo postoperatively. Although it does not affect vision in the short term, it can still cause pathological changes similar to that of epiretinal membrane formation. The ILM is composed of type IV, type VI and type VIII collagen, which is the basement membrane of Müller cells[2]. Removal of the ILM
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Figure 3 Manifestation of the eye 3 wk after the second vitrectomy. A: Three weeks after the second vitrectomy, optical coherence tomography showed that the macular hole was closed, covered by flocculent internal limiting membrane. The split of each layer was significantly reduced, and photoreceptor cells were absent in the macular area; B: Optomap: Tessellated fundus only was observed.

can affect the adhesion of Müller cells, leading to its dysfunction[8]. Therefore, the size of the preserved ILM in the macular region warrants further study.

The secondary MH was detected 1 wk after the initial vitrectomy. MH usually results from the natural progression of MF and is a common complication of vitrectomy[4]. The stiffness of Müller cells might considerably increase in MF, which might translate to higher mechanical force transmission to photoreceptors[9]. The inner retinal surface of the MF was vulnerable to developing a break, and tangential and anteroposterior traction between the vitreous and retina might induce MH formation[10]. Gao et al[11] investigated the possible mechanisms and risk factors for the development of secondary MH in MF based on preoperative OCT findings and found that a preoperative inner segment/outer segment (IS/OS) junction defect can be a risk factor for MH development. Kumar et al[12] found that vitrectomy with intraoperative OCT (I-OCT)-guided fovea-sparing ILM peeling helps in complete removal of traction, resolution of retinoschisis and good functional recovery, with fewer intraoperative and postoperative complications. Therefore, if preoperative OCT reveals an IS/OS junction defect, we should pay more attention to MH formation. Vitrectomy should be performed centripetal rather than centrifugal near the macula, and anteroposterior traction should be avoided to protect Müller cell processes and photoreceptor axons from damage. I-OCT may be used as it is associated with few intraoperative and postoperative complications.

In the present case, 5 mo after the initial vitrectomy, we observed a gradual reduction in the split range of the outer nuclear layer, a new split of the inner nuclear layer and gradual enlargement of the MH. The repair process of MF may be centripetal, gradually moving from the peripheral retina to macula. However, due to the expansion of the sclera in high myopia, the MH could not be closed. A new split was formed in the inner nuclear layer due to the longitudinal traction caused by the repair process of the outer nuclear layer and tangential traction caused by the epiretinal membrane in the residual ILM against retinal extension.

Vitrectomy combined with various auxiliary methods have been used to treat MH[7, 13]. Lai et al[7] repaired MH with retinal detachment in patients with high myopia by vitrectomy combined with ILM repositioning and autologous blood. Moreover, 96% of the MH was closed with the retina reattached after the first surgery, and 100% of the MH was closed with the retina reattached after the second surgery. Morizane et al[14] used a free autologous flap of the ILM to fill the MH and then covered it with low-molecular-weight viscoelastic material to repair the refractory MH, and the hole closure rate was 90%. Faria et al[15] reported that the external limiting membrane and ellipsoid zone were better repaired with inverted ILM covering in the MH than with inverted ILM filling the MH.

We treated the secondary MH successfully using 25-G vitrectomy combined with residual ILM inversion and covering of the MH and autologous blood. Fresh blood forms a blood clot within minutes, keeping the residual ILM flap inverted and covering the MH, thereby reducing the risk of dislocation after surgery[7]. The inverted ILM flap and blood clot mixture covering on the MH might seal the hole and provide a smooth surface for glial cell proliferation. The components and growth factors present in the blood could facilitate the healing processes of the MH. Additionally, the serum may reduce the toxic effects of indocyanine green staining of the ILM[16].
Our case report suggests that fovea-sparing ILM peeling provides a better chance to repair the secondary MH after initial vitrectomy. Additional cases need to be evaluated.

CONCLUSION

We consider that fovea-sparing ILM peeling can treat MF with fewer surgical complications effectively. When secondary MH develops after initial vitrectomy, the residual ILM in the macula can also provide better repair of the MH.

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Intervertebral bridging ossification after kyphoplasty in a Parkinson’s patient with Kummell’s disease: A case report

Jie Li, Yun Liu, Lei Peng, Jian Liu, Zhi-Dong Cao, Miao He

ORCID number: Jie Li 0000-0002-3286-2006; Yun Liu 0000-0001-7173-9732; Lei Peng 0000-0002-6192-3895; Jian Liu 0000-0003-1391-6715; Zhi-Dong Cao 0000-0002-9314-1421; Miao He 0000-0001-5295-0882.

Author contributions: Li J is the main writer of the article, that is, the first author; Li J, Liu Y, Peng L, Liu J, Cao ZD and He M designed the research study; Li J and Liu J performed the research; Li J, Liu Y, Peng L, Liu J, Cao ZD and He M analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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Abstract

BACKGROUND
The short-term therapeutic efficacy of kyphoplasty on Kummell’s disease is obvious. However, postoperative refracture and adjacent vertebral fracture occur occasionally and are difficult to treat. Parkinson’s disease (PD) is a pathological disorder associated with heterotopic ossification. In a patient with PD, an intervertebral bridge was formed in a short period of time after postoperative refracture and adjacent vertebral fracture, providing new stability.

CASE SUMMARY
A 78-year-old woman had been suffering from PD for more than 10 years. Three months before operation, she developed lower back pain and discomfort. The visual analog scale (VAS) score was 9 points. Preoperative magnetic resonance imaging indicated collapse of the L2 vertebra. Kyphoplasty was performed and significantly decreased the severity of intractable pain. The patient’s VAS score for pain improved from 9 to 2. Fifty days postoperatively, the patient suddenly developed severe back pain, and the VAS score was 9 points. X-ray showed L2 vertebral body collapse, slight forward bone cement displacement, L1 vertebral compression fracture, and severe L1 collapse. The patient was given calcium acetate capsules 0.6 g po qd and alfacalcidol 0.5ug po qd, and bed rest and brace protection were ordered. After conservative treatment for 2 mo, the patient's back pain was alleviated, and the VAS score improved from 9 to 2. Computed tomography at the 7-mo follow-up indicated extensive callus formation around the T12-L2 vertebrae and intervertebral bridging ossification, providing new stability.

CONCLUSION
Kyphoplasty is currently a conventional treatment for Kummell’s disease, with definite short-term effects. However, complications still occur in the long term,
and these complications are difficult to address; thus, the treatment needs to be selected carefully. To avoid refracture, an interlaced structure of bone cement with trabeculae should be created to the greatest extent possible during the injection of bone cement. Surgical intervention may not be urgently needed when a patient with PD experiences refracture and adjacent vertebral fracture, as a strong bridge may help stabilize the vertebrae and relieve pain.

Key Words: Kummell's disease; Parkinson's disease; Kyphoplasty; Refracture; Heterotopic ossification; Case report

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INTRODUCTION

Kummell's disease is characterized by vertebral collapse, pseudarthrosis, and progressive pain caused by ischemic osteonecrosis of the vertebral body[1]. Parkinson's disease (PD) is a pathological disorder associated with heterotopic ossification[2]. However, there have been no reports of PD causing intervertebral bridge formation. Currently, kyphoplasty is an effective surgery for the treatment of Kummell's disease[3]. However, occasional refracture of the vertebral body can seriously affect the prognosis of patients and is very difficult to treat[4].

In the present case, vertebral refracture and adjacent vertebral fracture after kyphoplasty resulted in persistent severe pain and dysfunction. These fractures were cured by extensive callus formation around the T12-L2 vertebrae, and intervertebral bridging ossification provided new stability.

CASE PRESENTATION

Chief complaints
A 78-year-old woman experienced severe low back recurrence pain 2 mo after kyphoplasty.

History of present illness
Two months before admission, the patient underwent kyphoplasty for Kummell's disease at L2, and the postoperative pain was significantly relieved. Two months after surgery, the patient experienced severe back pain recurrence in the same area. The radiographic findings indicated L2 refracture and new L1 fractures.

History of past illness
The patient had been suffering from PD of the rigidity type for more than 10 years. The stage of the patient was Hoehn and Yahr stage IV. She had been taking 600 mg levodopa and 150 mg benserazide hydrochloride orally daily to control the PD symptoms. The patient had significant standing instability when turning her body and
could not maintain balance when her body was pushed. Functionally, the patient’s mobility was significantly affected, and she could still walk and stand on her own, but she was unable to live independently.

**Personal and family history**
The patient had no previous or family history of similar illnesses.

**Physical examination**
The patient’s L1-2 spinous processes and pain on paravertebral muscle percussion were obvious, and lumbar movement was limited. No neurological injury was observed.

**Imaging examinations**
Preoperative magnetic resonance imaging (MRI) indicated collapse of the L2 vertebral body and the formation of an intravertebral cavity-like structure indicated by the arrows (Figure 1A). T2WI with fat suppression (T2WI FS) showed a fluid-filled intravertebral cavity, with little of the upper endplate structure remaining indicated by the arrows (Figure 1B). T2WI showed a low signal at the cavity edge, indicating vertebral bone necrosis and fibrous perichondrium formation, indicated by the arrows (Figure 1C and D).

Postoperative X-ray images showed that bone cement filled the cystic cavity of the L2 vertebral body with smooth edges, and there was insufficient bone cement dispersion outside the cystic cavity (Figure 2A and B). Fifty days postoperatively, X-ray images showed L2 vertebral body collapse, slight forward bone cement displacement (indicated by the black arrow), L1 vertebral compression fracture, and severe collapse (indicated by the orange arrow) (Figure 2C).

Seven-month follow-up CT indicated extensive callus formation around the T12-L2 vertebrae and intervertebral bridging ossification, providing new stability, as indicated by the arrow (Figure 3).

**Physical examination**
The patient’s L1-2 spinous processes and pain on paravertebral muscle percussion were obvious, and lumbar movement was limited. No neurological injury was observed.

**FINAL DIAGNOSIS**
The final diagnosis was Kummell's disease at L2, L2 vertebral refracture, and L1 vertebral compression fracture.

**TREATMENT**
Three months before admission, the patient developed lower back pain and discomfort and was hospitalized. The visual analog scale (VAS) score was 9 points. Preoperative MRI indicated collapse of the L2 vertebral body and the formation of an intravertebral cavity-like structure indicated by the arrows (Figure 1A). T2WI with fat suppression (T2WI FS) showed a fluid-filled intravertebral cavity, with little of the upper endplate structure remaining indicated by the arrows (Figure 1B). T2WI showed a low signal at the cavity edge, indicating vertebral bone necrosis and fibrous perichondrium formation, indicated by the arrows (Figures 1C and D).

Kyphoplasty was performed, and the severity of the intractable pain significantly decreased. Postoperative X-ray images showed that bone cement filled the cystic cavity of the L2 vertebral body with smooth edges, and there was insufficient bone cement dispersion outside the cystic cavity (Figure 2A and B). The patient’s VAS score for pain improved from 9 to 2. Fifty days postoperatively, the patient suddenly developed severe back pain, and the VAS pain score was 9 points. X-ray images showed L2 vertebral body collapse, slight forward bone cement displacement (Indicated by the black arrow), L1 vertebral compression fracture, and severe collapse (Indicated by the orange arrow) (Figure 2C).

The patient refused surgery, so she was given calcium acetate capsules (0.6 g po qd) and alfacalcidol (0.5 µg po qd), and bed rest and brace protection were ordered.
OUTCOME AND FOLLOW-UP

After conservative treatment for 2 mo, the patient's back pain was alleviated, and the VAS score improved from 9 to 2. CT at the 7-mo follow-up indicated extensive callus formation around the T12-L2 vertebrae and intervertebral bridging ossification, providing new stability, as indicated by the arrow (Figure 3).

Figure 1 Magnetic resonance imaging. A: Preoperative MRI indicated collapse of the L2 vertebral body and the formation of an intravertebral cavity-like structure indicated by the arrows; B: T2WI with fat suppression (T2WI FS) showed a fluid-filled intravertebral vacuum, with little of the upper endplate structure remaining indicated by the arrows; C and D: T2WI showed a low signal at the cavity edge, indicating vertebral bone necrosis and fibrous perichondrium formation, indicated by the arrows.
**DISCUSSION**

The refracture of cemented vertebrae, displacement of bone cement and fracture of adjacent vertebrae are rare complications after percutaneous kyphoplasty for Kummell's disease and are relatively difficult to address\(^5\). PD is a pathological disorder associated with heterotopic ossification\(^\text{6,7}\). There have been no reports in the literature on the occurrence or outcomes of postoperative complications in patients with both of these diseases at the same time.

**Cemented vertebral refracture**

Mckierman et al\(^8\) reported that osteonecrosis and pseudarthrosis are the main risk
factors for refracture. Due to the presence of fractures in the movable vertebrae, the bone cement tends to form a mass structure rather than spread throughout the trabecular bone[9]. During polymethyl methacrylate (PMMA) injection, the bone cement follows the path of least resistance through the intravertebral space, resulting in insufficient filling and a lack of interlacing with nearby bone tissue[10].

In addition, the formation of fibrous perichondrium at the internal edge of the vertebral cystic cavity prevented PMMA from forming an intersecting structure with the trabeculae[11] (Figure 1D). The stimulation of mechanical stress at the bone-cement interface may lead to microfractures of the vertebral body, highly progressive collapse of the vertebral body, failure at the bone-cement interface, and even fracture of the bone cement and collapse of the vertebral body[12]. Therefore, Heo et al.[13] proposed that vertebroplasty and kyphoplasty may be contraindicated by osteonecrosis or pseudoarthrosis of the fractured vertebral body.

**Adjacent vertebral body fracture**

After cementing the vertebral body, the protrusion of the endplate of the enhanced vertebral body increased as the height of the vertebral body was restored to a certain extent. At the same time, bone cement and residual endplates were fixed in the vertebral body adjacent to the endplate of the adjacent vertebral body. These factors lead to a lack of cushioning between adjacent vertebrae and bone cement, increasing the risk of refracture[14,15] (Figure 2C).

According to Fahim DK et al[16], the normal intervertebral disc, the endplate and part of the trabecular bone of the treated vertebral body act as buffers between the bone cement and adjacent vertebral body. When bone cement reaches the level of the intervertebral disc, the tissue buffer decreases or completely disappears, leading to a high rate of adjacent fractures. Baroud et al[17] found that bulging of the enhanced endplate results in hardening of the intervertebral joint and the entire motion segment. A high intervertebral pressure and an inward-facing endplate bulge may be responsible for adjacent fractures[18,19].

**Intervertebral bridging ossification**

Refractured vertebrae and adjacent fractured vertebrae are fused through intervertebral bridge formation at T12, L1 and L2 to achieve ultimate stability and significantly improve pain in patients within a short period (Figure 3).

PD has been described as a disease associated with HO incidence[6,7]. Namazi proposed a pathway by which PD mediates heterotopic ossification development[20]. In PD, peripheral blood mononuclear cells produce interleukin-1, interleukin-6, and tumor necrosis factor, which have been shown to play an important role in HO[21-24]. In addition, levodopa mediates ectopic ossification, has been found to stimulate bone formation, callus formation, and healing through growth hormone (GH), and has been used in vivo to promote bone growth after internal fixation of fractures[25-29].

The patient had PD for 10 years and was treated with oral levodopa and benserazide hydrochloride, so we hypothesized that the formation of her intervertebral bridge might be related to her disease and drug treatment. However, the existence of other interfering factors, such as the fracture itself, mechanical instability, blood leakage, and bone cement stimulation, which are all factors that stimulate the growth of fracture, cannot completely explain the formation of a large number of calli in a short period of time in patients with intervertebral bone bridges connecting three vertebrae[29]. More case studies and further laboratory studies may be needed to confirm this phenomenon.

**CONCLUSION**

Kyphoplasty is currently a common treatment for Kummell’s disease, with definite short-term effects. However, complications still occur in the long term, and these complications are difficult to address; thus, the treatment needs to be selected carefully. To avoid refracture, an interlaced structure of bone cement with trabeculae should be created to the greatest extent possible during the injection of bone cement. Surgical intervention may not be urgently needed when a patient with PD experiences refracture and adjacent vertebral fracture, as a strong bridge may help stabilize the vertebrae and relieve pain.
REFERENCES


Li J et al. Seven-month follow-up of vertebra refracture


CASE REPORT

Synovial chondromatosis of the hip joint in a 6 year-old child: A case report

Run-Bin Yi, Hao-Li Gong, Djandan Tadum Arthur, Jie Wen, Sheng Xiao, Zhong-Wen Tang, Feng Xiang, Kong-Jian Wang, Zhen-Qi Song

Abstract

BACKGROUND
Synovial chondromatosis (SC) is a rare benign lesion first reported by Ambrose Pare in 1558. It is most common in the knee joint, followed by the hip joint and elbow joint. It is characterized by the presence of multiple pearl-like osteochondral bodies in the joint. The incidence in children is extremely low.

CASE SUMMARY
We report a 6-year-old Chinese boy who presented to our hospital with left hip joint pain and claudication for more than one year. We performed total surgical resection of SC tissue in the left hip. A good prognosis was confirmed at the 6-wk follow-up. Pain and swelling symptoms were totally relieved, range of motion of his left hip returned to normal, and there was no clinical evidence of lesion recurrence at last follow-up. Our case is the youngest reported patient with SC occurring in the hip.

CONCLUSION
SC is a rare disease and can be easily misdiagnosed. When we encounter children with hip pain and claudication, increased vigilance and a comprehensive physical examination and imaging examination should be considered, in order to avoid misdiagnosis and delayed treatment in patients.

Key Words: Synovial chondromatosis; Child hip pain and claudication; Loose body; Good prognosis; Rare benign disorder; Case report

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INTRODUCTION

Pain accompanied by claudication is a common complaint of hip joint disease in children. Routine imaging examination is often nonspecific. Early and correct diagnosis has a marked influence on the prognosis and function of the hip joint in children.

Synovial chondromatosis (SC) is a benign tumor secondary to synovial chondroma. It occurs mostly in men aged 30-50 years and is very rare in children. SC can be classified into primary and secondary SC. Primary SC occurs with no history of osteoarticular diseases, while secondary SC occurs in the presence of pathological changes, such as osteoarthritis, rheumatoid arthritis, and bone degeneration[1]. SC frequently involves a single joint. The knee joint is the most commonly affected joint, followed by the hip joint, elbow joint, shoulder joint, and ankle joint; 33 areas have been reported to be involved[2]. The most common symptoms of SC are joint pain, swelling, and limited motion. Diagnosis is mainly based on imaging; Seventy percent of patients with SC have calcified nodules on X-ray and computed tomography (CT) examinations, while some patients may not have obvious calcification and nodules in the early stage.

A 6-year-old child with hip pain and claudication was admitted to our hospital. X-ray of the hip in this child was nonspecific. Combined with physical and magnetic resonance examinations, the patient was diagnosed with synoviochondroma of the left hip joint. SC was confirmed by surgery and pathologic examination.

CASE PRESENTATION

Chief complaints

A 6-year-old male patient was admitted to hospital due to left hip joint pain and claudication.

History of present illness

He was admitted to the hospital due to left hip joint pain and claudication for more than 1 year. He was diagnosed with left hip joint synovitis in other hospitals. He was advised to rest in bed, but his symptoms did not significantly improve. Later, he was diagnosed with left femoral head avascular necrosis and underwent external fixation with bracing. His symptoms did not significantly improve, and the pain and claudication were aggravated.

History of past illness

Past medical history was negative.

Personal and family history

Personal and family history, medication history, social history, and allergic history were negative.
**Physical examination**
No obvious swelling of the left hip joint was observed, with asymmetric groin lines, low skin temperature, local tenderness, pelvis tilting to the left, and unequal length of lower limbs of about 1.5 cm. The left hip joint internal rotation, external rotation, and flexion were limited, with left Allis sign (+), Thomas sign (+), and 4-character sign (+).

**Laboratory examinations**
Laboratory examinations were within normal ranges, including erythrocyte sedimentation rate, white blood cell count, and levels of C-reactive protein, rheumatoid factor, and tumor markers. Routine urinary testing was also normal.

**Imaging examinations**
B-ultrasound showed left hip joint effusion. X-ray showed slight flattening of the left femoral head (Figure 1A). CT showed a decrease in the density of the left hip joint epiphysis and widening of the left hip joint space (Figure 1B). Magnetic resonance imaging (MRI) showed synovial thickening of the left hip joint (Figure 1C).

**FINAL DIAGNOSIS**
Biopsy confirmed SC (Figure 2).

**TREATMENT**
The patient underwent an open biopsy and curettage of the lesion with orthopedic surgery under general anesthesia via a bikini incision of the left hip. After the skin tissue was cut, the hip capsule was revealed by turning down the rectus femoris through the gap between the tensor fasciae latae and the sartorius muscle. The hip capsule was cut along the acetabulum direction. Several irregular, milky white cartilage-like granules (Figure 3A) were seen in the articular cavity, with a maximum size of 2 cm × 2 cm × 0.5 cm. The hip joint was moved, and the cartilage particles were thoroughly cleaned. The hip joint was explored, the left femoral head was slightly flattened, and the synovial tissue showed proliferation and thickening. The sizes of the free bodies were different in block connection; the color was white or milky white; the surface was smooth (Figure 3B); the texture was tough, cartilage-like, and elastic; and the inside of the free bodies was solid without liquid outflow (Figure 3C).

**OUTCOME AND FOLLOW-UP**
After the surgery, the pain and limp symptoms disappeared. At the 6-wk follow-up, pain and limping had disappeared, and the range of motion of the hip joint was restored to a normal level.

**DISCUSSION**
SC is a rare benign lesion first reported by Ambrose Pare in 1558[3]. SC is most commonly seen in the knee joint, followed by the hip joint and elbow joint. It is characterized by the presence of multiple pearl-like osteochondral bodies in the joint.

Table 1 Previous pediatric cases reported as synovial chondromatosis in the English literature

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Location</th>
<th>Case number</th>
<th>Case age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carey[6], 1983</td>
<td>Knee</td>
<td>2</td>
<td>9, 10</td>
</tr>
<tr>
<td>Pelker et al[5], 1983</td>
<td>Knee</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Kistler[7], 1991</td>
<td>Knee</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Tiedjen[8], 2006</td>
<td>Knee</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Raza et al[9], 2014</td>
<td>Hip</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Manesh et al[10], 2017</td>
<td>Hip</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Wen et al[11], 2018</td>
<td>Hip</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

Figure 1 Radiology result of this patient. A: X-ray shows no specific findings, and the left femoral head epiphysis was slightly flattened; B: Computed tomography shows decreased density of the femoral head epiphysis in the left hip joint and a widened gap in the left hip joint; C: Magnetic resonance imaging shows the synovium around the left hip joint of the child was thickened and a part of the synovium was nodular.

synovial chondroma resection of the hip joint. In this case, after 6 wk of postoperative follow-up, the symptoms of pain and claudication disappeared, and the range of motion of the hip joint returned to normal. Our case was the youngest child with SC of the hip reported in the English literature. We performed open synovectomy and removal of the free bodies in the hip lesion; in a subsequent follow-up, his hip pain and claudication symptoms completely disappeared.

The etiology of cartilage tumors is not clear. It is speculated that the connective tissue under the synovial tissue metastasizes into cartilage cells, followed by cartilage ossification, to gradually produce cartilage nodules. These nodules are nourished by the joint fluid and gradually enlarge. Most of the cartilage nodules are later calcified or ossified. Milgram[12] described the classification of SC based on the location of intra-articular free bodies and pathological findings of synovial and free bodies. He described the first stage as an active intrasynovial lesion with microscopic metaplasia
Figure 2 Biopsy results confirmed synovial chondromatosis, hematoxylin-eosin staining showed active proliferation of chondrocytes.

Figure 3 Intraoperative findings of this patient. A: After incision of the joint capsule, a large number of free bodies in a milky white mass with irregular shapes were found in the joint; B: The free bodies varied in size, presented as massive connections, white or milky white in color, and a smooth surface; C: Free bodies are solid with no outflow of fluid.

of intrasynovial chondromatosis and no gross abnormalities. The second stage was a transitional intrasynovial lesion with synovial osteochondroma and free bodies. The pedicled cartilage bodies could be seen overhanging the synovial membrane without falling off. The third stage was the synovial lesion and the formation of cartilaginous or osteochondral free bodies. The difference in the present case was that obvious isolated bodies were not formed (Figure 3A), but lumps with irregular shapes developed. According to the classification by Milgram, we suggest that the lumps in our
case might be the previous form of synovial osteochondroma and free bodies in the second stage.

Imaging examination plays an important role in diagnosing synovial osteochondroma, with calcification occurring in 70%-95% of cases. Multiple calcifications were found in the capsule of the affected joint, which were usually smooth, round, and of different sizes; the imaging manifestations of free bodies with "annular and arc-shaped" chondroid mineralization strongly suggested SC[13]. In this case, no cartilaginous nodules and calcification were observed in the synovial tissue of the patient; also, no positive findings of the disease were reported during X-ray and CT examinations. This patient was misdiagnosed in several hospitals as transient synovitis of the hip or ischemic necrosis of the femoral head. The conventional MRI result showed the hip joint full of liquid, and the morphology of the free bodies was not specific enough to diagnose SC (Figure 1C). A study showed that dynamic T1-weighted imaging could be used along with intravenous chelation to enhance synovial tissue, and then to distinguish synovial tissue from SC[14]. Due to the dead area in the visual field of conventional hip arthroscopy, a single approach could not completely remove the pathological synovial tissue and the widely existing free bodies, thus easily leading to reoperation due to the high recurrence rate. Therefore, we chose open surgery to completely remove the pathological synovial tissue and free bodies. No signs of recurrence were noted, and satisfactory follow-up results were obtained. Therefore, it is also difficult to identify the hip joint effusion.

CONCLUSION

When we encounter children with hip pain and claudication, increased vigilance and comprehensive physical and imaging examinations should be considered, in order to avoid misdiagnosis and delayed treatment in patients.

REFERENCES

Orthodontic retreatment of an adult woman with mandibular backward positioning and temporomandibular joint disorder: A case report

Li-Yuan Yu, Kai Xia, Wen-Tian Sun, Xin-Qi Huang, Jing-Yu Chi, Ling-Jie Wang, Zhi-He Zhao, Jun Liu

Abstract

BACKGROUND
The role of occlusal factors on the occurrence of temporomandibular joint disorders (TMDs) is still unclear and it is tricky for orthodontists to treat malocclusions in patients with TMDs. We report the case of the second orthodontic treatment of an adult female with Class II division 2 malocclusion associated with TMD. With the removal of anterior occlusal interference, TMD symptoms were alleviated and cone beam computed tomography (CBCT) images showed the bilateral condyles shifted forward.

CASE SUMMARY
This case report presented an orthodontic retreatment of an adult female with TMD and mandibular backward positioning based on CBCT examination and Joint Space Index (JSI) analysis. The left and right JSI values of -38.5 and -52.6 indicated that the position of bilateral condyles had posterior displacement. Ten years prior to this evaluation, she underwent orthodontic treatment resulting in the extraction of two upper premolars and one lower central incisor. The joint symptoms, including pain and sounds, were alleviated along with verified mandibular forward repositioning by extraction of another lower central incisor.

CONCLUSION
Mandibular backward positioning could be associated with TMD. JSI analysis based on CBCT is a convenient way to examine condylar positions quantitatively.

**Key Words:** Cone beam computerized tomography; Joint Space Index; Temporomandibular joint disorder; Case report

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**Core Tip:** Class II division 2 malocclusion is considered to be a risk factor for temporomandibular joint disorders (TMDs). In this case of the second orthodontic treatment of an adult female with Class II division 2 malocclusion associated with TMD, we measured the joint space to assess the condylar position and found that the bilateral condyles were located in the posterior position. We suspected that this patient’s TMD was a manifestation of mandibular backward positioning. Temporomandibular joint symptoms were alleviated with the removal of anterior occlusal interference, and the posttreatment cone beam computed tomography images showed that bilateral condyles shifted forward after orthodontic treatment.

**INTRODUCTION**

Temporomandibular joint disorders (TMDs) are common public health problems and affect approximately 60% to 70% of people worldwide, according to statistics in different countries[1]. The clinical symptoms of TMDs include pain, joint sounds, and functional limitations, such as restricted mandibular movement and limited mouth opening[2]. Pain-related disorders can affect a patient’s social interactions, psychological health, and quality of life. Epidemiological researchers found that the prevalence of TMDs was associated with age, sex, occlusion, and orthodontic treatment[3,4]. However, the exact causes of TMDs are still largely unknown, and it is often difficult to find an obvious cause. Moreover, the role of occlusal factors in the occurrence of TMDs has remained controversial until recently[5]. Therefore, the treatment of malocclusion with TMDs is a complex problem for orthodontists.

Functional malocclusion was reported to cause displacement of the condyle in the glenoid fossa[6] and might result in functional disorders of the temporomandibular joint (TMJ)[7]. Condylar displacement could be a sign of functional deviation, which was analyzed by cone beam computed tomography (CBCT) and Joint Space Index (JSI) analyses in the treatment of mandibular shift in an adult woman[8]. As another example, Class II division 2 patients have salient features, including deep bites, retroclined upper incisors, and mandibular retrognathism[9]. It was reported that mandibular retrognathism in Class II division 2 patients would have a risk of articular disk displacement[10]. Nevertheless, there are few scientific reports about the pathology and treatment of functional malocclusion.

In this case, we reported orthodontic retreatment of an adult female with TMD and mandibular backward positioning based on CBCT examination and JSI analysis. The joint symptoms, including pain and sounds, were alleviated along with verified mandibular forward repositioning. Mandibular backward positioning could be related to TMD. Moreover, JSI analysis is a convenient way to examine condyle positions quantitatively.
**CASE PRESENTATION**

**Chief complaints**
An adult woman aged 26 years visited the clinic to request orthodontic retreatment for her relapsed crowding in her mandibular dentition.

**History of past illness**
Ten years prior to the present visit to the clinic, she received orthodontic treatment resulting in the extraction of two upper premolars and one lower central incisor.

---

**Table 1 Cephalometric analysis**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNA°</td>
<td>81.7 ± 2.5</td>
<td>82.4</td>
<td>82.2</td>
</tr>
<tr>
<td>SNB°</td>
<td>78.9 ± 2.2</td>
<td>79.5</td>
<td>79.9</td>
</tr>
<tr>
<td>ANB°</td>
<td>2.8 ± 1.2</td>
<td>2.9</td>
<td>2.3</td>
</tr>
<tr>
<td>SN-MP°</td>
<td>32.9 ± 4.2</td>
<td>34.8</td>
<td>34.2</td>
</tr>
<tr>
<td>U1-L1°</td>
<td>123.2 ± 6.2</td>
<td>136.8</td>
<td>129.2</td>
</tr>
<tr>
<td>U1-SN°</td>
<td>105.1 ± 6.2</td>
<td>82.8</td>
<td>101.3</td>
</tr>
<tr>
<td>U1-NA°</td>
<td>23.3 ± 6.2</td>
<td>15.8</td>
<td>17.6</td>
</tr>
<tr>
<td>L1-NB°</td>
<td>27.4 ± 4.7</td>
<td>28.1</td>
<td>26.0</td>
</tr>
<tr>
<td>IMPA (L1-MP)°</td>
<td>95.4 ± 4.7</td>
<td>93.0</td>
<td>91.5</td>
</tr>
<tr>
<td>UL-EP (mm)</td>
<td>-0.5 ± 1.9</td>
<td>-2.5</td>
<td>-1.7</td>
</tr>
<tr>
<td>LL-EP (mm)</td>
<td>1.3 ± 1.9</td>
<td>-2.2</td>
<td>-1.1</td>
</tr>
</tbody>
</table>


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**Figure 1 Pretreatment intraoral and facial photographs.**
Physical examination

The clinical examination revealed that the patient had a straight profile and a strong chin (Figure 1). A 2.0 mm space in the maxillary dentition and 4.0 mm of crowding in the mandibular dentition were found. The upper incisors were retroclined, and the anterior overjet was minimal. The anterior overbite was within the normal range. Compared with the facial midline, the maxillary dental midline deviated by 0.5 mm to the right. The mandibular dental midline was basically the center of the remaining lower central incisor since the other lower central incisor was missing. No chin deviation was found. She had Class II molar and canine relationships bilaterally.

Imaging examinations

Cephalometric analysis (Figure 2 and Table 1) indicated skeletal Class I malocclusion (SNA, 82.4°; SNB, 79.5°; ANB, 2.9°) with a normal mandibular plane angle (SN-MP, 34.8°). The maxillary incisors were retroclined (U1-SN, 82.8°; U1-NA, 15.8°).

The patient had experienced TMJ pain many times after her first orthodontic treatment, and we found joint clicking at the start of mouth opening in TMJ clinical examination. CBCT examination was performed to check the TMJs. CBCT examination was performed when the maxillary and mandibular teeth were in maximum intercuspation (MI). JSI was used to assess the condylar position by calculating the ratio of the anterior and posterior joint spaces[11]. Vargas-Pereira [12] described that the physiologic range of JSI values for the condylar position was -32.5 to 21.1. A greater value indicated an anterior position, while a smaller value indicated a posterior position. CBCT images of the TMJs were oriented sagittally and taken perpendicular to the maximum transverse of the long axis of the condylar region, as previously reported[13]. Left and right JSI values of -38.5 and -52.6 (Table 2), respectively, were obtained in this case. The results indicated that the position of bilateral condyles had posterior displacement and that the right condyle displacement was more severe than that of the left condyle. The right upper central incisor had dark gray discoloration, but the panorama examination showed no obvious findings. CBCT
Table 2 Joint space measurements

<table>
<thead>
<tr>
<th></th>
<th>Right temporomandibular joint</th>
<th>Left temporomandibular joint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anterior JS (mm)</td>
<td>Posterior JS (mm)</td>
</tr>
<tr>
<td>Pretreatment</td>
<td>3.57</td>
<td>1.11</td>
</tr>
<tr>
<td>Retention for 22 mo</td>
<td>3.28</td>
<td>1.30</td>
</tr>
<tr>
<td>Relative change (re-pre)</td>
<td>-0.29</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Re: Retention; pre, pretreatment; JS: Joint space; JSI: Joint space index.

examination revealed a large periapical radiolucency associated with the upper right central incisor (Figure 2). We collected the medical history and the patient gave no history of trauma, caries, and clinical symptoms of upper right central incisor. We speculated that the periapical periodontitis of the upper right central incisor might be associated with anterior occlusal interference.

**FINAL DIAGNOSIS**

The final diagnoses of the presented case were Class II malocclusion and TMD.

**TREATMENT**

In accordance with the pretreatment records and the patient's chief complaint, the treatment objectives were to: (1) Advise the endodontist to treat periapical periodontitis of the upper right central incisor; (2) Align the dental arch, eliminate dental crowding, and close the space; (3) Achieve ideal overjet and overbite as well as coincident dental and facial midlines; and (4) Prevent the aggravation of TMD and hopefully alleviate the TMD symptoms.

One possible option was nonextraction treatment. Three teeth were removed during the first orthodontic treatment, and only slight crowding relapse occurred in the anterior mandibular dentition. Too much space might be created if more teeth were extracted. Interproximal enamel reduction (IPR) was recommended in mild crowding [14]. Therefore, the lower anterior teeth might be grinded for the mandibular dentition alignment. However, there were some disadvantages. First, IPR was reported to have risks of tooth sensitivity and caries [14]. In addition, the overjet would still be minimal after the space in the upper dentition was closed and the lower dentition was aligned. It was also difficult to correct the Class II occlusion relationship without tooth extraction.

Class II elastics are widely used for Class II malocclusion treatment; these elastics are conducive to correcting deep anterior overbite, closing the extraction space, and guiding the mandible forward. However, caution should be taken when treating hyperdivergent patients and those exhibiting progressive absorption of the condyle. In this case, the patient had a normal mandibular plane angle and posterior displacement of the condyle but no joint absorption. Class II elastics could guide the mandible forward to obtain a Class I occlusion relationship and change the position of the condyle, which might ease TMJ symptoms. However, when using Class II elastic traction, a larger overjet is required to prevent occlusal trauma in anterior teeth. Therefore, Class II elastics could not be used with the above treatment option.

The other treatment option was to extract one lower central incisor. Since two upper premolars and one lower central incisor were extracted in the first orthodontic treatment, the removal of another lower central incisor was beneficial to establish a coordinated and symmetrical dental arch. However, after aligning and closing the space in the upper and lower dentition, it was not clear if the anterior overjet would be too large. There was an advantage to using Class II elastics to correct molar relationships in this option while guiding the mandible forward to change the position of the condyle and establish an ideal anterior overjet. Based on the consideration of the treatment objectives, this option was chosen for this case.
Before orthodontic treatment, the patient received endodontic therapy, and the periapical periodontitis of the upper right central incisor was controlled. After extraction of the mandibular central incisor, the 0.022 × 0.028-inch slot preadjusted edgewise brackets were then bonded onto the entire dentition except for the second molars and the third molars. The archwire sequence progressed from 0.014-inch nickel-titanium wire to 0.018 × 0.025-inch stainless steel working wire. Seventeen months into treatment, all teeth were leveled and aligned, and space closure was completed. Although the use of Class II elastics had been planned, the occlusal relationship was corrected once an adequate anterior overjet was established, and Class II elastics were not actually applied. CBCT examination was performed to assess the recovery of 11 and changes in condylar positions. The total treatment time was 17 mo. A Hawley retainer was used for retention.

**OUTCOME AND FOLLOW-UP**

The posttreatment photographs showed a Class I canine and molar relationship, normal overbite and overjet, improved midline deviation, and neatly aligned teeth (Figure 3). The posttreatment panoramic radiograph showed no significant root resorption and good root parallelism (Figure 4). CBCT examination of 11 indicated the healing of periapical radiolucent lesions around the root of the upper right central incisor (Figure 4). The posttreatment cephalometric analysis is shown in Table 1. Superimposition of the pretreatment and posttreatment cephalometric radiographs showed mild retraction of the mandibular incisors and proclination of the upper incisors (Figure 5). The CBCT images of the TMJs in the aforementioned section showed the condyles shifted forward after orthodontic treatment (Figure 6 and Figure 7). The right JSI after 22 mo of retention was -43.2 and was larger than that observed at pretreatment (-52.6), which confirmed the condylar shifted forward (Table 2). Although the CBCT image showed an incompetent left condylar after 22 mo of retention, we inferred a larger JSI of the left condylar. CBCT superimposition of the pretreatment and retention bilateral TMJs also validated the same results (Figure 8). Joint clicking disappeared, and TMJ pain was relieved. After 22 mo of retention, the patient visited the clinic for tooth bleaching of the upper right central incisor. Facial and intraoral photographs showed a stable occlusion (Figure 9), and CBCT images showed the TMJ in a stable position without recurrence of TMJ pain and sound...
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Figure 4 Posttreatment radiographs and cone beam computed tomography image of the upper right central incisor.

Figure 5 Superimposition of pretreatment (black) and posttreatment (red) cephalometric tracings.

(Figures 6 and 7).

DISCUSSION

Functional or occlusal factors are considered a potential etiology of TMDs. It has been proposed that the presence of occlusal interferences usually results in TMJ functional
disorders. Previous studies reported that occlusal interference could cause mandibular deviation, leading to changes in the condylar position and pain in the TMJ[15]. Hidaka et al[6] also commented that functional malocclusion from malocclusions or orthodontic treatments led to condylar displacement in the glenoid fossa. It was speculated that unstable occlusion increased the load of the mandibular condyle and articular fossa, which might affect TMJ morphology[16]. The latter might also interfere with mandibular functional movement. It was confirmed that eliminating functional occlusal factors could relieve dysfunction of the masticatory system[17].

Many scholars, such as Roth[18], advocated for functional occlusion as the goal of orthodontic treatment. The authors believed that more attention should be given to achieving centric relation and MI harmony without occlusal interference after orthodontic treatment. Articulator mountings, including a Panadent condylar position indicator and mandibular position indicator[19], were designed to transfer the occlusal status and the condylar position to the outside of the mouth. The traditional method is to diagnose occlusal interference and premature contact and to detect functional displacement of the condyle. However, it was reported that this method could not accurately quantify small changes in joint position[20,21].

Imaging examination is an essential method for the diagnosis and treatment of TMDs. Various imaging examinations can be used to detect the TMJ, such as panoramic radiography, magnetic resonance imaging (MRI) and CBCT. The latter two methods can be used for quantitative analysis. MRI has excellent sensitivity in nonmineralized tissue and is widely used to evaluate cartilage and disc position and to diagnose TMD[22]. Although the quality of MRI has improved, there are still limitations in the low-quality images of the complex bone structure of the TMJ that it provides[23]. In addition, MRI evaluation was not easily accepted by patients due to high costs; also, stomatological hospitals are rarely equipped with MRI equipment. Maxillofacial CBCT is specially designed for the maxillofacial tissue. Maxillofacial CBCT was developed from conventional CT and is specially designed for maxillofacial tissues with low cost and a low radiological dose[24]. CBCT is an intuitive, simple and accurate method for comprehensive evaluation of hard tissue, diagnosis of condylar changes, and a clear display of joint space in three dimensions[25].

Figure 6 Cone beam computed tomography images of the right TMJ in the sagittal (upper) and transverse (lower) planes. A: Pretreatment; B: Posttreatment; C: 22-mo retention.
Figure 7 Cone beam computed tomography images of the left TMJ in the sagittal (upper) and transverse (lower) planes. A: Pretreatment; B: Posttreatment; C: 22-mo retention.

Figure 8 Cone beam computed tomography superimposition of pretreatment (gray) and 22-mo retention (green) bilateral temporomandibular joints.

Mandibular retrognathism is usually associated with Class II division 2, and such patients are more susceptible to TMDs[9]. It was reported that adults with Class II malocclusion might experience muscle pain[26], and another study found that mandibular retrognathism in Class II division 2 patients increased the risk of articular disk displacement[10]. In this case, the patient extracted two upper premolars and one lower central incisor in the first orthodontic treatment, resulting in a minimal overjet to restrict mandibular movement and Class II division 2 malocclusion. We preliminarily estimated TMD risk based on medical history and TMJ clinical examination. CBCT was performed to evaluate the condyle position. Many researchers, such as
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Mavreas[27] and Ruf[13,28], recommended the use of the JSI to evaluate anterior and posterior joint spaces and condylar positions. Vargas-Pereira[12] calculated the physiologic range of the JSI (-32.5, 21.1), indicating positive anterior displacement and a negative posterior displacement[11]. We used the JSI to examine joint space in CBCT images and found that the bilateral condyles were located in the posterior position. Combined with the medical history, TMJ clinical examination, intraoral occlusion, and CBCT images, we suspected that the minimal overjet in the first orthodontic limited mandibular movement, led to backward positioning of the mandible, and caused TMJ symptoms. Therefore, the patient's TMD might be a consequence of functional mandibular retraction. In the second orthodontic treatment, with the proclination of upper anterior teeth and retraction of lower anterior teeth to construct an ideal overjet, joint symptoms were alleviated without using Class II elastic traction. Comparing the CBCT images of the TMJ before and after the second treatment, it was found that bilateral condyles shifted forward, which further suggested that occlusal factors might be closely associated with the patient's TMD. After 22 mo of retention, the condylar position was stable, and there was no recurrence of TMD.

The patient's TMD could be due to iatrogenic functional or occlusal factors during the first orthodontic treatment. Although the relationship between orthodontics and TMDs has been controversial, several studies have reported that incorrect orthodontic treatment results in iatrogenic TMDs. For example, it was reported that excessive retraction and retroclination of upper incisors could cause premature contacts and lead to distal displacement of the mandible and mandibular condyle. As a result, mandible retraction increases the risk of TMDs[29]. Therefore, more attention should be given to joint changes in orthodontic treatment.

CONCLUSION

In conclusion, mandibular backward positioning could be correlated with TMD and TMD symptoms might be alleviated with the mandibular forward repositioning for this situation. JSI analysis based on CBCT is convenient to evaluate condylar positions quantitatively.

Figure 9 Intraoral and facial photographs after 22 mo of retention.
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CASE REPORT

Autosomal recessive spinocerebellar ataxia type 4 with a VPS13D mutation: A case report

Xin Huang, Dong-Sheng Fan

ORCID number: Xin Huang 0000-0002-1764-4537; Dong-Sheng Fan 0000-0002-3965-7718.

Author contributions: Huang X collected all the data, recorded the video, performed the literature review, and wrote the manuscript; Fan DS reviewed and revised the manuscript; all authors issued final approval for the version to be submitted.

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Abstract

BACKGROUND
Autosomal recessive spinocerebellar ataxia type 4 (SCA4) is a type of SCA that is a group of hereditary diseases characterized by gait ataxia. The main clinical features of SCA4 are progressive cerebellar ataxia, pyramidal signs, neuropathy, and macrosaccadic intrusions. To date, many gene dysfunctions have been reported to be associated with SCA4.

CASE SUMMARY
Here, we report a novel compound heterozygous mutation, c.3288delA (p.Asp1097ThrfsTer6), in the VPS13D gene in a young female Chinese patient. The patient found something wrong with her legs about 10 years ago and presented with the typical characteristics of SCA4 when she came to the hospital, including ataxia, neuropathy, and positive pyramidal signs. She was then diagnosed with SCA4 and went home with symptomatic schemes.

CONCLUSION
SCA4 is a hereditary disease characterized by ataxia, pyramidal signs, neuropathy, and macrosaccadic intrusions. We report a novel compound heterozygous mutation, c.3288delA (p.Asp1097ThrfsTer6), in the VPS13D gene, which enriches the gene mutation spectrum and provides additional information about SCA4.

Key Words: Spinocerebellar ataxia; Recessive; VPS13D gene; Compound heterozygous mutation; Case report

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Core Tip: We report a female Chinese patient diagnosed with autosomal recessive spinocerebellar ataxia type 4 (SCAR4) with a compound heterozygous mutation, c.3288delA (p.Asp1097ThrfsTer6), in the VPS13D gene. By reviewing the literature, we speculate that the mutation may cause SCAR4 by affecting mitochondrial function. However, there is currently no specific treatment for SCAR4.

INTRODUCTION
Spinocerebellar ataxia (SCA) is a group of hereditary diseases characterized by progressive gait ataxia, dysarthria, and oculomotor disorders[1-4], which can be caused by autosomal dominant, autosomal recessive, or X-linked mutations[5]. Autosomal recessive SCA (SCAR) represents the type of SCA caused by autosomal recessive mutations. To date, 13 types of SCAR (named SCAR1-13) have been reported[6], and we focused on SCAR4 in the present study. SCAR4 is characterized by cerebellar ataxia, pyramidal signs, neuropathy, and macrosaccadic intrusions, generally developing in early adulthood[7]. SCAR4 has been reported to be caused by many gene mutations, and mutations in the vacuolar protein sorting–associated protein 13D isoform 1 (VPS13D) gene represent the essential component[7]. However, the details of the mechanism have not been explored thoroughly. Here, we report a case of SCAR4 with a novel compound heterozygous mutation in the VPS13D gene.

CASE PRESENTATION
Chief complaints
A 33-year-old Chinese woman came to our department for not being able to run for 10 mo.

History of present illness
The patient felt tired when standing up from squatting and walking downstairs 10 years ago, but daily life was not affected at that time. After that, she had increasingly more difficulties in these actions in the following days. Five years ago, she could not walk steadily even on a level road. Ten months ago, she realized that she could not run anymore. No muscle atrophy or fasciculation was found.

History of past illness
The patient had no previous history of neurological disorders, and she did not suffer any significant injuries in these years.

Personal and family history
The patient was born in Beijing and had no remarkable family history. Her parents and sister were clinically healthy (Figure 1).

Physical examination
On physical and neurological examination, the patient had an unsteady walk and an ataxic gait. Other cerebellar signs, such as nystagmus, nose-finger test, and heel-shin slide, were normal. Additionally, she could not stand up when squatting. Her tendon reflexes were hyperactive in the lower limbs. Bilateral Babinski signs, Hoffmann signs, and a Rossolimo sign in the left hand were also observed. There was no problem with muscle strength or sensory examination.

Laboratory examinations
There were increases in the levels of anti-CCP, anti-Ro52, and ANA. However, we
could not determine what type of immune system disease that the patient had even with the help of physicians in the Department of Rheumatology because she did not have any related symptoms. Cerebrospinal fluid analysis was normal.

**Imaging examinations**

Electroneuronography showed reduced amplitude of sensory potentials in the right median nerve. Magnetic resonance imaging of the brain (Figure 2) showed no obvious abnormality, and lumbar MRI showed only mild hyperostosis.

**Gene sequence analysis**

To explore the underlying genetic patterns, we communicated with the patient and obtained informed consent for whole exon sequencing. We collected venous blood samples from the patient and her family at Peking University Third Hospital. We identified a novel compound heterozygous pathogenic mutation, c.3288delA (p.Asp1097ThrfsTer6; RefSeq NM_015378)/c.12485C>A (p.Thr4162Asn; RefSeq NM_015378), in the *VPS13D* gene in this patient. Her father was found to be heterozygous for the c.3288delA frameshift mutation, and her mother was found to be heterozygous for the c.12485C>A missense mutation in the *VPS13D* gene (Figure 3). Her parents reported no symptoms, which suggested that the disease was inherited in an autosomal recessive mode. Although there was also a c.6575C>T (p.Thr2192Ile; RefSeq NM_001376) missense variant in the *DYNC1H1* gene in this patient, but this variant may be clinically irrelevant.

**FINAL DIAGNOSIS**

The final diagnosis of this patient was SCAR4.

**TREATMENT**

The treatment of SCA has always been a difficult problem worldwide. However, there have been several clinical trials in recent years. There is no specific treatment for SCA to date. Currently, the treatment for the patient is mainly rehabilitation therapy.

**OUTCOME AND FOLLOW-UP**

The patient returned to the neurologic clinic regularly. She complained of worsening ataxia last time she returned in July 2021. We plan to continue the follow-up in the following years.

**DISCUSSION**

The clinical manifestations of SCAR are varied, including slowly progressive gait disorder, hypotonia, excessive clumsiness, etc.[8]. Similarly, SCAR mostly occur before the age of 30 years[2-9]. SCAR4, one type of SCAR, mainly presents with cerebellar ataxia and hypotonia.
Figure 2 Brain magnetic resonance imaging. The image on the left is the T1-weighted axial image, the image in the middle is the T2-weighted axial image, and the image on the right is the T2-weighted sagittal image. No cerebellar atrophy was observed.

Figure 3 Genomic sequence electropherograms. The patient carried a novel c.3288delA (p.Asp1097ThrfsTer6) frameshift mutation of the VPS13D gene, which was not detected in Chinese databases. Only the patient’s father was heterozygous for this mutation among her parents and sister, and her mother was heterozygous for c.12485C>A (p.Thr4162Asn). Pedigree analysis suggested that the disease was consistent with autosomal recessive inheritance.

ataxia, neuropathy, pyramidal signs, and macrosaccadic intrusions[7]. The patient’s clinical presentation was consistent with the diagnosis of SCAR4. First, the patient developed symptoms early as her symptoms appeared at 22 years old and became evident at 32 years old. The main symptoms were unsteady walking and clumsiness when walking. In addition, the patient felt tired quickly before the unsteady walk. Consistently, the phenomena of pre-ataxia were confirmed by two earlier observational studies, which found other symptoms occurring several years before ataxia[10]. Pyramidal signs, as identified by physical examination, and neuropathy, as observed by electroneuronography, provided evidence consistent with the diagnosis. Because we did not perform electronystagmograms, we could not confirm the saccadic intrusions. Overall, the patient’s clinical manifestations were in accordance with SCAR4.

Currently, the diagnosis of SCAR4 relies on genetic testing[11]. SCAR4 is mapped to chromosome 16q22.1, and the VPS13D gene has been reported to be closely related to SCAR4[7]. In this case, we found a novel compound heterozygous mutation in the VPS13D gene, c.3288delA (p.Asp1097ThrfsTer6; RefSeq NM_015378)/c.12485C>A (p.Thr4162Asn; RefSeq NM_015378). Pedigree analysis suggested that the disease was autosomal recessive inherited. This mutation has not been described in the previous literature. Furthermore, the new mutation is located in a relatively conserved domain, suggesting that the variant may be a pathogenic mutation (Figure 4).

VPS13D (NM_015378.3) consists of 69 exons spanning approximately 281000 nucleotides, and it encodes a 4388 amino acid protein (NP_056193.2)[12,13]. Although large, VPS13D is intolerant to variations[14]. Only 27 individuals from 15 families have been identified with VPS13D mutations (Figure 5)[7,14-18]. Previous studies have reported that VPS13D gene variants could lead to normal growth and development
Figure 4 Conservation of amino acids in the context of the frameshift mutation. Amino acid sequence alignments of some of the amino acids affected by the mutation are shown for selected species. The red rectangle highlights the first amino acid affected by the frameshift mutation. This novel mutation is located in a relatively conserved domain.


VPS13D is an important protein involved in mitochondrial metabolism, including autophagy (mitophagy), fission, and clearance in Drosophila [18,19]. VPS13D is also essential in human cells. Researchers have observed enlarged mitochondria in human HeLa cells with VPS13D knockout [20]. Gauthier et al. [12] reported that T2 hyperintensities in the basal ganglia and/or white matter could be observed on brain MRI in VPS13D-caused movement disorders. Considering that mitochondrial leukodystrophies also show a pattern of diffuse subcortical white matter and bilateral basal ganglia involvement, we suggest that the impact of VPS13D mutation on mitochondrial function may be part of the pathophysiological mechanisms of these diseases [14].

CONCLUSION

To date, studies on SCAR4 are insufficient with only a few reported cases. Nonetheless, SCAR4 shows genetic heterogeneity and the pathogenesis and treatment are far from clear at present. It is necessary to collect data on mutations in the VPS13D gene and to further explore the correlations between genotype and phenotype. We report a female Chinese patient diagnosed with SCAR4 with a compound heterozygous mutation, c.3288delA (p.Asp1097ThrfsTer6), in the VPS13D gene, which enriches the gene mutation spectrum and is valuable information for SCAR4. The physiopathological mechanism of the gene variant requires further investigation.

REFERENCES


Primary adrenal diffuse large B-cell lymphoma with normal adrenal cortex function: A case report

Zhi-Nan Fan, Hong-Jin Shi, Bo-Bo Xiong, Jin-Song Zhang, Hai-Feng Wang, Jian-Song Wang

ORCID number: Zhi-Nan Fan 0000-0003-4547-4202; Hong-Jin Shi 0000-0001-9883-270X; Bo-Bo Xiong 0000-0001-6121-9565; Jin-Song Zhang 0000-0003-3271-3454; Hai-Feng Wang 0000-0003-0360-1402; Jian-Song Wang 0000-0002-2140-1618.

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Zhi-Nan Fan, Hong-Jin Shi, Bo-Bo Xiong, Jin-Song Zhang, Hai-Feng Wang, Jian-Song Wang, Department of Urology, The Second Affiliated Hospital, Kunming Medical University, Kunming 650000, Yunnan Province, China

Corresponding author: Jin-Song Zhang, Doctor, Department of Urology, The Second Affiliated Hospital, Kunming Medical University, No. 374 Dianmian Avenue, Wuhua District, Kunming 650000, Yunnan Province, China. 945933392zjs@sina.com

Abstract

BACKGROUND
Diffuse large B-cell lymphoma, which accounts for about approximately 30% to 40% of non-Hodgkin's lymphomas, is the most common type and is a class of aggressive B-cell lymphomas. However, diffuse large B-cell lymphomas primary to the adrenal gland are rare.

CASE SUMMARY
A 73-year-old man was admitted with abdominal pain and fatigue. After admission, enhanced adrenal computed tomography indicated irregular masses on both adrenal glands, with the larger one on the left side, approximately 8.0 cm × 4.3 cm in size. The boundary was irregular, and surrounding tissues were compressed. No obvious enhancement was observed in the arterial phase. Resection of the left adrenal gland was performed. Pathological diagnosis revealed diffuse large B-cell lymphoma. After surgery, the patient received R-CHOP immunochemotherapy. During the fourth immunochemotherapy, patient condition deteriorated, and he eventually died of respiratory failure.

CONCLUSION
R-CHOP is the conventional immunochemotherapy for primary adrenal diffuse large B-cell lymphoma. Surgery is mainly used to diagnose the disease. Hence, the ideal treatment plan remains to be confirmed.

Key Words: Large B-cell lymphoma; Adrenal glands; Immunochemotherapy; Surgical procedures; Case report

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Core Tip: Primary adrenal diffuse large B-cell lymphoma is a rare disease with no consistent treatment standards. The R-CHOP regimen is the conventional immunochemo therapy regimen for this disease. We report a case of surgery combined with immunochemo therapy; however, immunochemo therapy was ineffective and the patient eventually died of respiratory failure. Therefore, the optimal treatment of primary adrenal diffuse large B-cell lymphoma remains to be further explored.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL), which accounts for approximately 30% to 40% of non-Hodgkin’s lymphoma, is the most common type among the aggressive B-cell lymphomas[1]. Diffuse large B-cell lymphomas that originate in the adrenal glands are rare. Primary adrenal DLBCL (PADLBCL) is a highly malignant tumor with no specific clinical manifestations and thus, requires early diagnosis and treatment. The main manifestations of PADLBCL in patients are abdominal pain, fatigue, fever, night sweats, weight loss, and adrenal cortex insufficiency. Imaging often shows adrenal occupancy; however, clear diagnosis requires adrenal biopsy or postoperative specimen examination. To date, no unified treatment standard exists, and PADLBCL is mainly treated with immunochemo therapy, and yet has poor prognosis. Currently, there have been only few reports on PADBCLD. We here report a case of bilateral PADLBCL. Combined with related literature and our observations, we have analyzed the clinical, imaging, and pathological characteristics of PADLBCL, and discussed the current related treatment methods and prognostic factors, with an aim to deepen the understanding of this disease.

CASE PRESENTATION

Chief complaints
A 73-year-old man was admitted in our hospital with abdominal pain and fatigue lasting 1 mo.

History of present illness
One month before his admission, the patient developed persistent abdominal pain without obvious incentives, such as tolerable dull pain on the left side, without abdominal distension, lethargy, cold sensitivity, itchy skin, and change in skin color, among other symptoms. Since the start of the symptoms, the patient had poor appetite and spirit, and lost more than 10 kg weight.

History of past illness
The patient had no history of surgery, trauma, or other diseases.

Personal and family history
There was no history of hereditary diseases. No family members had similar symptoms.

Physical examination
The physical examination of the patient was unremarkable.

Laboratory examinations
Routine blood tests, liver and kidney function test, blood coagulation function test, hormone-related examination, and tumor marker analysis showed no obvious
abnormalities. In addition, the level of serum potassium was normal.

**Imaging examinations**
The adrenal enhancement computed tomography (CT) scan showed the presence of irregular masses in the adrenal glands on both sides, with the larger one being located on the left side. Its size was approximately 8.0 cm × 4.3 cm, its border was irregular, and the surrounding tissues were compressed. We did not observe any obvious enhancement in the arterial phase, nor any obvious swollen lymph nodes were noted later on (Figure 1).

**FINAL DIAGNOSIS**
The patient was diagnosed with non-GCB primary adrenal diffuse large B-cell lymphoma.

**TREATMENT**
We performed a left adrenalectomy under laparoscopic surgery. During the surgery, an irregular mass was observed in the left adrenal area. The mass was strongly adhered to the upper pole of the left kidney, and it pressurized the left kidney in forward and downward direction. No detectable lymph node enlargement was observed. The upper pole of the left kidney was damaged during the laparoscopic separation of the mass, so the wound surface was sutured continuously with 3-0 absorbable suture. After the separation of the tumor from the upper pole of the left kidney, due to excessive blood on the wound surface and compromised visibility, the tumor vessels were perturbed during the operation leading to the rupture of associated blood vessels. Due to the excessive blood loss, the laparoscopic surgery was reallocated to open abdominal surgery. The intraoperative blood loss was approximately 1300 mL, and blood transfusion was prescribed to overcome the loss.

**OUTCOME AND FOLLOW-UP**
Pathological diagnosis identified the presence of non-GCB diffuse large B-cell lymphoma in the left adrenal gland. Light microscopy observation revealed diffuse infiltration and growth of tumor cells in normal adrenal tissues. Tumor cells were composed of medium to large lymphoid cells. Most cells were round or oval in shape, double chromotropic or basophilic, containing less cytoplasm and larger nuclei (Figure 2A and B). Immunohistochemical analysis revealed tumor cells to be CD19 (+), CD20 (+), PAX-5 (+), CD79a (+), Ki67 (70%), CD43 (+), MUM1 (+), bcl-6 (+), CD45RO (focus +), CD3 (scattered +), cyclinD1 (-), CD10 (-), and CD30 (-) (Figure 2C and D). After the pathological diagnosis was confirmed, the patient was immediately notified telephonically. However, due to the patient’s personal reasons, the return visit was delayed, and the patient returned to the hospital for further treatment a month later. Re-examination of the patient with abdominal enhanced CT 1 mo after the surgery revealed multiple soft tissue shadows in the retroperitoneum on both sides, uneven enhancement, and a left retroperitoneal soft tissue mass protruding into the kidney (Figure 3). Subsequently, the patient underwent four immunochemotherapy sessions at the hematology department of our hospital. The immunochemotherapy regimen was R-CHOP (rituxan 600 mg d1; cyclophosphamide 1.2 g d1; liposomal adriamycin 40 mg d1; vincristine 4 mg d1; and prednisone acetate 100 mg d1-d5). During fourth immunochemotherapy session, the patient developed a severe pulmonary infection, and sputum culture suggested infection by fungi and multidrug-resistant bacteria. The patient coughed sputum, and his body temperature fluctuated between 37 and 38 °C, and therefore, he was treated with sensitive antibiotics. Chest CT indicated diffuse patchy fuzzy shadows in both lungs, indicating inflammation. Hematologists did not rule out lung damage caused by immunochemotherapy drugs, and symptomatic treatment was continued. On January 22, 2019, the patient was required to receive 9 L/min oxygen by mask, with his oxygen saturation being 85%. Re-examination of the chest CT revealed further aggravation of the infection. Antibiotic treatment and oxygen therapy were strengthened further, with the oxygen saturation of the patient reaching 92%. Subsequent treatment continued according to patient’s symptoms.
Figure 1 Preoperative abdominal enhanced computed tomography. A: Irregular masses were observed in the bilateral adrenal glands, with the larger masses being located on the left side, with a size of approximately 8.0 cm $\times$ 4.3 cm. No obvious enhancement was noted in the enhanced arterial phase, whereas uneven enhancement was observed in the portal phase. B: The left mass was surrounded the left renal artery, compressing the upper pole of the left kidney and part of the left renal vein. The boundary was irregular, while no obvious enlarged lymph nodes were found behind the peritoneum.

Figure 2 Pathological section. A: Hematoxylin & eosin (HE, $\times$ 100). Diffuse infiltration and growth of tumor cells; B: HE ($\times$ 200). Tumor cells were composed of medium to large lymphoid cells, most of which were round and oval, double chromotropic or basophilic, containing less cytoplasm and large nuclei; C: Immunohistochemical SP method of CD20 staining. Strong positively stained cell membrane in all tumor cells (the brownish yellow part of the picture); D: Immunohistochemical SP method of CD20 staining. Strong positively stained cell membrane in all tumor cells (the brownish yellow part of the picture).

However, at 03:37 on January 27, 2019, his oxygen saturation dropped to 60%. His oxygen saturation could not be monitored further, his heart rate decreased gradually, and his both pupils were dilated. The patient was declared dead and the cause of his death was determined as respiratory failure.
**DISCUSSION**

PADLBCL is a rare disease. To date, only more than 100 cases have been reported in the PubMed database[2]. PADLBCL mainly affects middle-aged and elderly men, with an average age of more than 60 years, and a male-to-female sex ratio of 2.93:1. In addition, the bilateral involvement of adrenal glands is common[3]. At present, the etiology and pathogenesis of PADLBCL remain unclear and have been suggested to be related to autoimmune deficiency, HIV, or EBV infections[4]. There are two viewpoints regarding the pathogenesis of PADLBCL. First, it may be related to the genetic predisposition of patients, such as mutations in the p53 and c-kit encoding genes as reported in adrenal lymphomas[5]. The second view suggests the initial occurrence of lymphoma outside the adrenal glands followed by their subsequent affliction, with chemokines and microRNAs driving this process, which can explain the bilateral involvement of the adrenal glands[6].

The clinical manifestations of PADLBCL lack specificity. Most patients experience pain around the waist and abdomen as the first symptom, accompanied by fatigue, fever, and night sweats[7]. When the bilateral adrenal glands are involved, most patients can have symptoms of adrenal insufficiency, manifested as skin pigmentation, hypotension, and fever[8]. In addition, PADLBCL involves the hypothalamic-pituitary axis, leading to adrenal insufficiency[9]. Therefore, for PADLBCL with adrenal insufficiency, systematic endocrine assessment should be performed. As our patient had PADLBCL with normal adrenal cortex function, his case relied on imaging examinations, providing lesser diagnostic information from the clinical symptoms and signs.

Imaging is an indispensable auxiliary diagnostic tool for PADLBCL, and the commonly used clinical examinations include CT and magnetic resonance imaging (MRI)[10]. In particular, in CT PADLBCL usually manifests as a low-density adrenal mass, which is moderately enhanced during enhanced scanning, revealing necrosis. In contrast, MRI examination shows a T1 phase low signal and T2 phase high signal. The T1 phase low signal can be distinguished from the T1 phase high signal caused by the hemorrhage of adrenal sarcoma. Besides, FDG-PET is more accurate in evaluating tumors and involved parts for determining extra-adrenal lesions[11,12]. In this case, only a CT examination was performed. However, it is deemed necessary to perform FDG-PET examinations in all PADLBCL cases. Moreover, histopathological examination are required for final diagnosis.

Pathological examination remains the gold standard for the diagnosis of PADLBCL. More specifically, observation under a light microscope reveals the destruction of the adrenal tissue structure, often accompanied by large lamellar necrosis and diffuse infiltration of large lymphocytes. In addition, immunohistochemical analysis of cells often reveals the expression of the CD19, CD20, CD22, CD45, CA79a, and PAX5 markers, and sometimes the expression of CD10 and CD5 proteins. In particular, CD5+ lymphomas are more malignant and associated with a poor prognosis[13]. Immuno-
Fan ZN et al. Non-GCB primary adrenal DLBCL

hastochemistry can also be used to classify the molecular types of PADLBCL. For this purpose, Hans algorithm is most extensively used in routine practice, and it consists of three markers (CD10, Bcl6, MUM1). Based on the combination of these three markers, Hans algorithm could divide DLBCL into two groups (GCB and non-GCB subtype) [14]. Non-GCB type PADLBCL is clinically common and often related to poor prognosis[15]. In recent years, studies have reported that non-GCB patients are often characterized by a higher expression of the proliferation index (Ki-67), with standard R-CHOP immunochemotherapy regimen being less effective in such patients[16]. However, other studies have reported that R-CHOP immunochemotherapy may achieve complete remission of PADLBCL[8].

Combining the medical history of the patient, imaging, pathological morphology, and immunophenotype facilitates the correct diagnosis of PADLBCL; however, attention should be paid to exclude the following possibilities: (1) Secondary lymphoma, that is, that no other lymphomas existed before diagnosis; and (2) Other adrenal tumors including adrenocortical carcinoma, pheochromocytoma, malignant melanoma, and neuroendocrine tumors. Early diagnosis of PADLBCL is generally difficult until the tumor has grown substantially and compresses the peripheral nerves or organs, causing corresponding symptoms or damage to the adrenal tissue and adrenal insufficiency.

Currently, there is no unified treatment regimen for PADLBCL. Most of the therapeutic strategies are developed based on the summary and comparison of the treatment experiences of lymphoma. PADLBCL is usually treated as a systemic disease, and early diagnosis and treatment can significantly prolong the patient’s survival. Since lymphoma is a systemic disease, the invasiveness of PADLBCL is generally extends beyond the visual limit, and it is difficult to achieve complete resection. Therefore, surgery is mainly used to diagnose the disease, and further immunochemotherapy is recommended post-surgery. R-CHOP immunochemotherapy is generally recommended as the first choice, and rituximab combined with second-line chemotherapy, such as bendamustine, DAEOCH, DHAP, GDP, and GEMOX, is recommended for patients with relapsed/refractory PADLBCL. Patients with relapsed/refractory PADLBCL are known to exhibit a generally rapid progress of the disease and cannot tolerate chemotherapy drugs[17].

As mentioned, PADLBCL has a poor prognosis, Kim et al[18] reported 31 cases of primary adrenal DLBCL with overall 2-year and progression-free survival rates of 68.3% and 51.1%, respectively. A few reports have reported that patients with PADLBCL receiving R-CHOP immunochemotherapy have a better prognosis and can achieve long-term remission or even complete remission[8,19]. It has also been reported that the treatment of surgery, chemotherapy, and autologous peripheral blood stem cell transplantation could retain a patient in remission for 2 years[20]. Many factors, such as the IPI score, non-GCB type, pathological type, treatment of the patient abandonment, and non-standard treatment can affect the prognosis of patients. In addition, adrenal lymphoma is one of the major risk factors for the recurrence of central nervous system (CNS) lymphoma[21]. In the study by Kim et al[18], 13% of patients with adrenal lymphoma had CNS lymphoma recurrence. Therefore, systemic methotrexate or intrathecal injection of methotrexate may be administered during the treatment to prevent the involvement and recurrence of the central nervous system.

In this case, preoperative examination indicated normal adrenal cortex function, which impeded the preliminary diagnosis of PADLBCL by the physician-in-charge. Postoperative pathology indicated non-GCB PADLBCL, and the patient received R-CHOP immunochemotherapy; however, the effect of immunochemotherapy was not beneficial. Possibly, the age of the patient and the impact of the disease and chemotherapy resulted in impaired immune response, leading to the patient acquiring severe lung infection and dying of respiratory failure.

CONCLUSION

The incidence of PADLBCL is low, and clinical symptoms are not typical. It is necessary to improve CT and FDG-PET examinations used for the evaluation of tumor staging, which would be helpful in standardizing treatment. Conventional immunochemotherapy includes the R-CHOP regimen, and surgery is mainly used to diagnose the disease, while the prevention of central nervous system lymphoma also needs to be considered. Thus, the ideal treatment plan needs to be strategized based on further research.
Compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.


Varicella-zoster virus-associated meningitis, encephalitis, and myelitis with sporadic skin blisters: A case report

Ken Takami, Tsuneaki Kenzaka, Ayako Kumabe, Megumi Fukuzawa, Yoko Eto, Shun Nakata, Katsuhiro Shinohara, Kazunori Endo

Abstract

BACKGROUND
Varicella-zoster virus (VZV) generally causes chickenpox at first infection in childhood and then establishes latent infection in the dorsal root ganglia of the spinal cord or other nerves. Virus reactivation owing to an impaired immune system causes inflammation along spinal nerves from the affected spinal segment, leading to skin manifestations (herpes zoster). Viremia and subsequent hematogenous transmission and nerve axonal transport of the virus may lead to meningitis, encephalitis, and myelitis. One such case is described in this study.

CASE SUMMARY
A 64-year-old man presented with dysuria, pyrexia, and progressive disturbance in consciousness. He had signs of meningeal irritation, and cerebrospinal fluid (CSF) analysis revealed marked pleocytosis with mononuclear predominance and a CSF/serum glucose ratio of 0.64. Head magnetic resonance imaging revealed hyperintense areas in the frontal lobes. He had four isolated blisters with papules and halos on his right chest, right lumbar region, and left scapular region. Infected giant cells were detected using the Tzanck test. Degenerated epidermal cells with intranuclear inclusion bodies and ballooning degeneration were present on skin
biopsy. Serum VZV antibody titers suggested previous infection, and the CSF tested positive for VZV-DNA. He developed paraplegia, decreased temperature perception in the legs, urinary retention, and fecal incontinence. The patient was diagnosed with meningitis, encephalitis, and myelitis and was treated with acyclovir for 23 days and prednisolone for 14 days. Despite gradual improvement, the urinary retention and gait disturbances persisted as sequelae.

CONCLUSION
VZV reactivation should be considered in differential diagnoses of patients with sporadic blisters and unexplained central nervous system symptoms.

Key Words: Varicella-zoster virus; Encephalitis; Meningitis; Myelitis; Central nervous system; Case report

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Core Tip: We describe a rare case of multiple central nervous system (CNS) complications following varicella zoster virus (VZV) reactivation in an immunocompetent patient with mild diabetes. He had four isolated blisters with encephalitis, meningitis, and myelitis. VZV reactivation should be considered in the differential diagnosis of patients with sporadic blisters and unexplained CNS symptoms.

INTRODUCTION
The varicella-zoster virus (VZV) generally causes chickenpox at its first infection in childhood and then establishes latent infection in the dorsal root ganglia of the spinal cord or other nerves[4]. When reactivated owing to impaired systemic immune function, the virus causes inflammation along the spinal nerves from the spinal segment affected by the latent infection, leading to skin manifestations (herpes zoster) [1]. Viremia and subsequent hematogenous transmission and nerve axonal transport of the virus may lead to meningitis, encephalitis, and myelitis[2].

Upon VZV reactivation, viremia is usually absent[3], and viral particles are transported via the nerves. However, in immunocompromised hosts, skin lesions can be more extensive and severe, and viral replication in epithelial cells may result in viremia[4]. In severely immunocompromised hosts, VZV can be disseminated to the lungs, liver, central nervous system (CNS), and other tissues. Myelitis is a relatively common complication of herpes zoster[3] and is considered to be caused by the spread of VZV from the dorsal root ganglia to the spinal cord at the spinal level affected by skin rashes[6].

Here, we report about a very rare case of concurrent meningitis, encephalitis, and myelitis caused by VZV reactivation in a patient with just a few blisters.

CASE PRESENTATION

Chief complaints
Fever, progressive disturbance in consciousness.

History of present illness
The patient was a 64-year-old man. He was transported by ambulance with urinary retention and pyrexia of > 38 °C that persisted for several days as well as progressive disturbance in consciousness.
History of past illness
He did not have regular health checkups and there was no significant medical history. He had an uncertain history of chickenpox in childhood and no history of varicella vaccination. He tested negative for human immunodeficiency virus (HIV) and had no history of bone marrow transplantation or other known conditions associated with immunosuppression.

Personal and family history
He had consumed 540 mL of Japanese sake (60 g of alcohol) and smoked 20 cigarettes per day since the age of 20 years.

Physical examination
The patient’s body temperature was 37.2 °C, blood pressure was 182/107 mmHg, heart rate was 106 beats/min and regular, and his respiratory rate was 21 breaths/min; and SpO₂ of 99% in room air. Neurological examination showed a Glasgow Coma Scale score of E4V3M5, pupils equal in size (3 mm/3 mm), round, and reactive to light (+/+), positive nuchal rigidity, and negative Kernig’s sign. The tendon reflexes were markedly increased, predominantly in the lower extremities, with a positive Babinski sign bilaterally. There was no obvious quadriplegia.

Skin findings included four isolated and sporadic blisters with red papules and a red halo in the right anterior/Lateral chest, right lumbar region, and left scapular region (Figure 1).

Laboratory examinations
We detected infected giant cells using the Tzanck test and degenerated epidermal cells with intranuclear inclusion bodies and ballooning degeneration on skin biopsy of blisters in the right chest (Figure 2); these findings were consistent with VZV infection.

Mild increase in blood glucose levels (174 mg/dL) and HbA1c level (6.8%) suggestive of diabetes were noted. No increase in inflammatory response was observed (White blood cell count 5800 cells/µL, C-reactive protein 0.15 mg/L). There was no evidence of impaired humoral immunity with a negative HIV antibody test. Serum VZV antibody titers were 75.9 (+) for VZV immunoglobulin G (IgG) (EIA) and 0.49 (−) for VZV immunoglobulin M (IgM) (EIA), which is a pattern indicative of a previous infection. Cerebrospinal fluid (CSF) analysis (Table 1) showed marked pleocytosis with mononuclear predominance, with no decrease in the CSF/serum glucose ratio (0.64). The CSF tested positive for VZV-DNA with $1.4 \times 10^6$ copies/mL.

Imaging examinations
For symptoms associated with frontal lobe disorders such as altered personality and talkativeness that occurred after admission, the patient underwent plain head magnetic resonance imaging (MRI) on hospital day 3 (Figure 3). Diffusion-weighted imaging revealed hyperintensities in the bilateral frontal lobes. Although not evident immediately after admission, paraplegia became apparent after private room isolation was discontinued and rehabilitation was started. Decreased thermal nociception and urinary retention and rectal disturbances were also noted.

Contrast-enhanced thoracolumbar MRI (Figure 3) performed on hospital day 14 showed diffuse enhancement of the meninges at Th9 to L5 with lumbar predominance and no enhancement of the cord itself. Concurrent myelitis was diagnosed based on the diagnostic criteria proposed by the Transverse Myelitis Consortium Working Group[7] although contrast-enhanced MRI of the thoracolumbar spine showed no clear enhancement of the spinal cord.

FINAL DIAGNOSIS
Based on these findings, we diagnosed meningitis, encephalitis, and myelitis caused by VZV reactivation.

TREATMENT
Treatment was initiated with 500 mg acyclovir intravenously three times a day (for 23 days) and prednisolone at 60 mg (1.5 mg/kg)/d (tapered, for 14 days), resulting in a gradual improvement of symptoms.
Table 1 Results of cerebrospinal fluid analysis on admission

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient’s value</th>
<th>Reference value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Light yellow</td>
<td>Clear</td>
</tr>
<tr>
<td>Xanthochromia</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Cell count (cells/μL)</td>
<td>484</td>
<td>0–3</td>
</tr>
<tr>
<td>Monocyte count (cells/μL)</td>
<td>448</td>
<td>0–3</td>
</tr>
<tr>
<td>Neutrophil count (cells/μL)</td>
<td>36</td>
<td>0–3</td>
</tr>
<tr>
<td>Total protein (mg/dL)</td>
<td>788</td>
<td>10–40</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>111</td>
<td>50–75</td>
</tr>
<tr>
<td>HSV antibody titer (CFT)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HSV-DNA (PCR) (copies/mL)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>VZV antibody titer (CFT)</td>
<td>4</td>
<td>Negative</td>
</tr>
<tr>
<td>VZV-DNA (PCR) (copies/mL)</td>
<td>$1.4 \times 10^6$</td>
<td>Negative</td>
</tr>
</tbody>
</table>

CFT: Complement fixation test; HSV: Herpes simplex virus; PCR: Polymerase chain reaction; VZV: Varicella-zoster virus.

Figure 1 The skin lesion on the right chest.

Figure 2 Skin biopsy of the lesion on the right chest. The lesion shows intranuclear inclusion bodies and ballooning degeneration.

Changes in the serum VZV antibody titer and CSF analysis results are shown in Table 2. Results of the CSF analysis showed a steady decrease in cell count, and on hospital day 16, the CSF was confirmed to be negative for VZV-DNA. The CSF VZV antibody titer increased more than 8-fold. Regarding serum VZV antibody titers, a significant increase in IgG was noted, whereas no apparent IgM seroconversion was observed. Symptoms of frontal lobe disorders improved with treatment. Plain head MRI performed on hospital day 39 revealed the disappearance of the frontal lobe
### Table 2 The patient’s clinical course

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>9</th>
<th>16</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF cell count (cells/μL)</td>
<td>484</td>
<td>112</td>
<td>119</td>
<td>29</td>
</tr>
<tr>
<td>CSF VZV antibody titer (CFT)</td>
<td>4</td>
<td></td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>CSF VZV-DNA (PCR) (copies/mL)</td>
<td>$1.4 \times 10^6$</td>
<td>$3.2 \times 10^2$</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>Serum VZV-IgM (EIA)</td>
<td>0.49 (-)</td>
<td>0.95 (+)</td>
<td>0.44 (-)</td>
<td></td>
</tr>
<tr>
<td>Serum VZV-IgG (EIA)</td>
<td>75.9 (+)</td>
<td>$&gt; 128$ (+)</td>
<td>$&gt; 128$ (+)</td>
<td></td>
</tr>
</tbody>
</table>

CSF: Cerebrospinal fluid; VZV: Varicella-zoster virus; CFT: Complement fixation test; PCR: Polymerase chain reaction; IgM: Immunoglobulin M; EIA: Enzyme immunoassay; IgG: Immunoglobulin G.

**Figure 3** Axial diffusion-weighted magnetic resonance imaging on day 3 and sagittal contrast-enhanced T1-weighted magnetic resonance imaging on day 14. A: The images show hyperintensities in the bilateral frontal lobes (block); B: Diffuse enhancement of meninges (arrows) with lumbar predominance and no cord enhancement.

Hyperintensities. The patient continued rehabilitation and showed a slight improvement in condition. However, the urge to urinate did not recover. In addition, gait disturbance and urinary retention associated with myelitis persisted as sequelae.

### OUTCOME AND FOLLOW-UP

On hospital day 60, the patient was transferred to another hospital for continued rehabilitation. Two months after the transfer, the patient developed lacunar infarction which was treated conservatively. Thereafter, he continued rehabilitation and was discharged home with an activities of daily living grade corresponding to independent wheelchair operation.

### DISCUSSION

In this case report, the patient with mild diabetes but no apparent immunodeficiency developed meningitis, encephalitis, and myelitis owing to VZV reactivation. This was a very rare case with only sporadic blisters accompanied by multiple CNS complications. CNS involvement has been reported as a rare complication of VZV infection, with an incidence of 0.1%–0.3% and 35% in immunocompetent and immunocompromised individuals, respectively[8]. Our literature search found only a few cases of multiple CNS complications caused by VZV, including eight cases of concurrent meningitis, encephalitis, and myelitis[8-14].

The early detection of blisters on emergency arrival led to a strong suspicion and early diagnosis of VZV meningitis in our case. Concurrent myelitis was diagnosed based on the diagnostic criteria proposed by the Transverse Myelitis Consortium Working Group[7] although contrast-enhanced MRI of the thoracolumbar spine showed no clear enhancement of the spinal cord. Despite the prompt initiation of
We reported a rare case of concurrent meningitis, encephalitis, and myelitis owing to VZV reactivation. Table 3 compares the eight previously reported cases of concurrent meningitis, encephalitis, and myelitis caused by VZV reactivation with our case. Although CNS complications of VZV infection are more common in immunocompromised individuals, no underlying disease was identified in three cases. These patients had no predisposing factors for immunosuppression, such as acquired immunodeficiency syndrome, prior organ transplant, or use of oral immunosuppressants. Therefore, it is likely that decreased immunity caused by aging and other factors led to the reactivation of VZV. Among the previously reported cases, only one patient had a skin rash with C8-Th3 distribution. The other seven patients presented neurological complications of VZV without skin symptoms, which is consistent with zoster sine herpete (ZSH). Our patient had only four sporadic blisters with no band-like cluster of skin eruptions. Bilateral blisters are an uncommon dermatological manifestation of VZV in geriatrics, but his disseminated herpes zoster caused bilateral sporadic skin eruptions. The simultaneous onset of meningitis, encephalitis, and myelitis could occur in immunocompetent patients, with none or a few eruptions rather than typical herpes zoster.

The skin rash in our patient appeared like a chickenpox rash, and the possibility of reactivation with VZV was also considered. However, a high serum VZV-IgG level on admission and the absence of VZV-IgM seroconversion over time suggested that VZV reactivation was more likely the cause. Generally, herpes zoster does not manifest itself in an immunocompetent host, and whether lesions are formed depends on the host’s immune status. In the event of virus reactivation, individuals with an active immune system may develop ZSH with only prodromal pain and no skin lesions. A previous report documented that 44% of patients with VZV infection in the CNS had no skin rash. In ZSH, CD4+ T cells and CD8+ memory T cells expressing skin-homing receptors are considered to provide innate immunity to suppress the spread of VZV between skin cells, thereby preventing skin rash manifestation. The number of skin eruptions caused by VZV correlates with the amount of virus in circulation before their manifestation, and therefore, delayed occurrence of an immune response can lead to the deeper and broader spread of the viral infection and severe lesions. The number and severity of skin eruptions were low in our patient, probably owing to the low viral load in circulation because the skin eruptions were caused by reactivation, not reinfection, of the virus from the previous infection.

Patients with mild skin rash may develop severe illness, similar to our patient. This highlights the importance of early recognition of blisters through skin examination of the entire body and considering VZV infection as a differential diagnosis even if the patient has isolated and sporadic blisters. It is also important to consider VZV infection when diagnosing a patient with unexplained CNS symptoms.
VZV reactivation in a 64-year-old patient with mild diabetes but with no apparent immunodeficiency. The patient had a small number of blisters. Based on our case findings, VZV infection should be considered a differential diagnosis in patients with sporadic blisters or unexplained CNS symptoms.

REFERENCES


Table 3 Summary of studies on VZV-associated meningitis, encephalitis, and myelitis

<table>
<thead>
<tr>
<th>Case</th>
<th>First Author (yr)</th>
<th>Ref</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Underlying diseases</th>
<th>Rash</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mancardi (1987)</td>
<td>8</td>
<td>32</td>
<td>F</td>
<td>None</td>
<td>None</td>
<td>Acyclovir</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>Kleinschmidt-DeMasters (1996)</td>
<td>9</td>
<td>69</td>
<td>F</td>
<td>Steroid dependent asthma</td>
<td>C8-Th3 distribution</td>
<td>Not reported</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>Kleinschmidt-DeMasters (1996)</td>
<td>9</td>
<td>36</td>
<td>M</td>
<td>HIV</td>
<td>None</td>
<td>Not reported</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>Cinque (1997)</td>
<td>10</td>
<td>Not reported</td>
<td>Not reported</td>
<td>HIV</td>
<td>None</td>
<td>Acyclovir</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>Sissoko (1998)</td>
<td>11</td>
<td>75</td>
<td>M</td>
<td>None</td>
<td>None</td>
<td>Acyclovir</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>Russman (2003)</td>
<td>12</td>
<td>51</td>
<td>F</td>
<td>Steroid dependent CREST syndrome</td>
<td>None</td>
<td>Acyclovir</td>
<td>Survived</td>
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<tr>
<td>7</td>
<td>Tavazzi (2008)</td>
<td>13</td>
<td>85</td>
<td>F</td>
<td>Steroid dependent SLE</td>
<td>None</td>
<td>Acyclovir</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>Tizazu (2020)</td>
<td>14</td>
<td>53</td>
<td>M</td>
<td>Mild diabetes mellitus</td>
<td>Four sporadic blisters</td>
<td>Acyclovir</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>Takami (2021)</td>
<td>Present case</td>
<td>64</td>
<td>M</td>
<td>Mild diabetes mellitus</td>
<td>Four sporadic blisters</td>
<td>Acyclovir</td>
<td>Survived</td>
</tr>
</tbody>
</table>

HIV: Human immunodeficiency virus; SLE: Systemic lupus erythematosus; F: Female; M: Male.
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Tension pneumocephalus following endoscopic resection of a mediastinal thoracic spinal tumor: A case report

Chao-Yuan Chang, Cheng-Che Hung, Ju-Mien Liu, Cheng-Di Chiu

ORCID number: Chao-Yuan Chang 0000-0002-6112-9495; Cheng-Che Hung 0000-0001-6461-6312; Ju-Mien Liu 0000-0001-5025-9166; Cheng-Di Chiu 0000-0003-0369-0935.

Author contributions: Chiu CD designed the study; Liu JM and Hung CC acquired the patient’s data; Chang CY analyzed and interpreted the data and drafted the manuscript; Chang CY and Chiu CD revised the manuscript critically for important intellectual content; all authors read and approved the final manuscript.

Informed consent statement: The patient has provided informed consent for publication of this case report and any accompanying images.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Supported by: China Medical University Hospital (No. DMR-107-063).

Country/Territory of origin: Taiwan

Abstract

BACKGROUND
Pneumocephalus is a rare complication presenting in the postoperative period of a thoracoscopic operation. We report a case in which tension pneumocephalus occurred after thoracoscopic resection as well as the subsequent approach of surgical management.

CASE SUMMARY
A 66-year-old man who received thoracoscopic resection to remove an intrathoracic, posterior mediastinal, dumbbell-shaped, pathology-proven neurogenic tumor. The patient then reported experiencing progressively severe headaches, especially when in an upright position. A brain computed tomography scan at a local hospital disclosed extensive pneumocephalus. Revision surgery for resection of the pseudomeningocele and repair of the cerebrospinal fluid leakage was thus arranged for the patient. During the operation, we traced the cerebrospinal fluid leakage and found that it might have derived from incomplete endoscopic clipping around the tumor stump near the dural sac at the T3 level. After that, we wrapped and sealed all the possible origins of the leakage with autologous fat, tissue glue, gelfoam, and duraseal layer by layer. The patient recovered well, and the computed tomography images showed resolution of the pneumocephalus.

CONCLUSION
This report and literature review indicated that the risk of developing a tension pneumocephalus cannot be ignored and should be monitored carefully after thoracoscopic tumor resection.

Key Words: Tension pneumocephalus; Neurogenic tumor; Thoracoscope; Case report

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CASE PRESENTATION

Chief complaints
A 66-year-old man described suffering from severe headache and vomiting, which became exaggerated with postural changes, following treatment with thoracoscopic resection to remove a neurogenic tumor.

History of present illness
The symptoms appeared starting on the 7th postoperative day.

History of past illness
The patient was previously diagnosed with a thoracic spinal dumbbell tumor.

Personal and family history
None.

Physical examination
The patient was sent to our emergency department, where a neurological examination showed clear consciousness (Glasgow coma scale: E4V5M6) with drowsiness and disorientation, no cranial nerve abnormalities, and full muscle power in all four limbs. Preoperatively, the patient’s body temperature was 36.4 °C, blood pressure was

Preoperatively, the patient’s body temperature was 36.4 °C, blood pressure was 120/80 mmHg, heart rate was 72 bpm, and respiratory rate was 18 breaths per minute. The patient was alert and oriented to time, place, and person. Physical examination revealed no abnormalities except for dizziness and headache.

The patient was sent to our emergency department, where a neurological examination showed clear consciousness (Glasgow coma scale: E4V5M6) with drowsiness and disorientation, no cranial nerve abnormalities, and full muscle power in all four limbs. Preoperatively, the patient’s body temperature was 36.4 °C, blood pressure was

Tension pneumocephalus (TP) is defined as the presence of air in the intracranial space, causing intracranial hypertension and a mass effect[1,2]. The clinical presentation of TP may include headache, nausea, vomiting, vertigo, aphasia, hemiparesis, altered levels of consciousness, and frontal lobe syndrome[1-4]. Because most symptoms associated with TP are non-specific, the diagnosis primarily depends on imaging findings. The formation of TP can be fatal if not diagnosed early and treated properly[5].

Spinal dumbbell tumors accounted for 17% to 22% of all spinal cord tumors according to previous reports[6,7] and are classified as epidural, intradural, or paravertebral depending on the locations involved[6]. Laminectomy with costotransversectomy has been presented as an effective method for the resection of thoracic dumbbell tumors involving large intraspinal and paraspinal regions[8,9]. Anterior approaches may also be feasible for the treatment of tumors that only involve the paraspinal region[10]. However, complications may develop after surgery, including pleural injury, bleeding, damage to the spinal cord, and cerebrospinal fluid leakage[8-10]. Few cases have been reported regarding the occurrence and management of pneumocephalus following the thoracoscopic resection of a neurogenic tumor[11,12]. We report a case in which TP developed after a thoracoscopic resection and describe the subsequent surgical management approach.

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Because intraoperative repair is difficult to assess.

Core Tip: Pneumocephalus is a rare complication that presents during the postoperative period following a thoracoscopic resection of spinal dumbbell tumors. Here, we present a potential method for resolving tension pneumocephalus and present our detailed experiences following the thoracoscopic resection of a posterior mediastinal dumbbell tumor, together with a review of the literature. The risks of experiencing pneumocephalus following thoracoscopic resection for a spinal tumor cannot be neglected because intraoperative repair is difficult to assess.

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Figure 1 Computed tomography scans of the patient’s brain showing tension pneumocephalus. A: Non-contrast views of preoperative brain computed tomography images; B-C: Images of axial (B) and sagittal view (C) show progressive tension pneumocephalus, pneumoventricle, and air leak in the spinal canal.

Figure 2 Pre-operative evaluations. A-B: T2-weighted magnetic resonance imaging in axial view (A) and fast spin echo, fat-suppression coronal view (B) showing a cystic pouch laterally surrounding the spinal nerve root at left T3 level (arrow), which may be derived from the neural foramen of the L3 level. The air-fluid level was also demonstrated (arrow); C) Axial view of chest computed tomography showing pneumothorax and subcutaneous emphysema (arrow); D) Poorly healing previous thoracoscopic access wound.

145/73 mmHg, heart rate was 90 bpm, and respiratory rate was 16 breaths per minute. The patient had normal heart and clear lungs sounds.

Laboratory examinations
Before the surgery, the patient presented with normal white blood cell, neutrophil, lymphocyte, and monocyte counts, and slight decreases in red blood cell count (3.48 × 10^6/µL), hemoglobin concentration (11.0 g/dL), and hematocrit level (31.7%) were detected.

Imaging examinations
A brain computed tomography scan demonstrated TP and pneumoventricle with the air extending down into the intraspinal space, and the progression of TP was found 3 d after his admission to the intensive care unit (Figure 1). A magnetic resonance imaging scan of the thoracic spine disclosed a left T2/T3 pseudomeningoele with air-fluid level, while a chest computed tomography demonstrated pneumothorax and subcutaneous emphysema around the poorly healing previous thoracoscopic access.
Table 1 Reported cases which pneumocephalus developed after surgical treatments for spinal or posterior mediastinal tumor

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Article type</th>
<th>Cases with pneumocephalus</th>
<th>Histology</th>
<th>Spinal region</th>
<th>Relation to dura</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trujillo-Reyes et al., 2014</td>
<td>Case report</td>
<td>1/1</td>
<td>Schwannoma</td>
<td>Thoracic</td>
<td>ND</td>
</tr>
<tr>
<td>Huang et al, 2005</td>
<td>Case report</td>
<td>1/1</td>
<td>Neurilemmoma</td>
<td>Thoracic</td>
<td>ND</td>
</tr>
<tr>
<td>Nam et al, 2019</td>
<td>Case series</td>
<td>18/20</td>
<td>Schwannoma (n = 16)/Meningioma (n = 4)</td>
<td>Cervical (15%)/Thoracic (60%)/Lumbar (25%)</td>
<td>IDEM</td>
</tr>
<tr>
<td>Kim et al, 2008</td>
<td>Case report</td>
<td>1/1</td>
<td>Myxopapillary ependymoma</td>
<td>Lumbar</td>
<td>IDEM</td>
</tr>
<tr>
<td>Özdemir et al, 2017</td>
<td>Case report</td>
<td>1/1</td>
<td>ND</td>
<td>Lumbar</td>
<td>IDEM</td>
</tr>
<tr>
<td>Bilsky et al, 2000</td>
<td>Case report</td>
<td>1/3</td>
<td>Neurofibroma</td>
<td>Thoracic</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: No data; IDEM: Intradural-extradural.

Table 2 Reported cases which pneumocephalus developed after surgical treatments for spinal or posterior mediastinal tumor

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Surgical approach</th>
<th>Clinical symptoms</th>
<th>CSF leakage</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trujillo-Reyes et al., 2014</td>
<td>VATS</td>
<td>Headache, vomiting</td>
<td>ND</td>
<td>Bed rest, oxygen</td>
</tr>
<tr>
<td>Huang et al, 2005</td>
<td>VATS</td>
<td>Headache, progressive loss of consciousness</td>
<td>Postoperative chest tube drainage amount increased</td>
<td>Bilateral frontal burr hole, Trendelenburg position</td>
</tr>
<tr>
<td>Nam et al, 2019</td>
<td>Posterior (laminectomy+durotomy)</td>
<td>Headache</td>
<td>Intraoperative duratomy and primary suture with artificial dural and fibroblastic glue</td>
<td>Bed rest, analgesics</td>
</tr>
<tr>
<td>Kim et al, 2008</td>
<td>Posterior (laminectomy+durotomy)</td>
<td>Headache, restless</td>
<td>Intraoperative duratomy and primary suture with fibroblastic glue</td>
<td>Bed rest, hydration</td>
</tr>
<tr>
<td>Özdemir et al, 2017</td>
<td>Posterior (laminectomy+durotomy)</td>
<td>Headache, nausea, vomiting</td>
<td>ND</td>
<td>Bed rest, hydration</td>
</tr>
<tr>
<td>Bilsky et al, 2000</td>
<td>Posterior/lateral thoracotomy</td>
<td>Lethargy, confusion</td>
<td>Postoperative chest tube drainage amount increased</td>
<td>Discontinue chest tube, bed rest</td>
</tr>
</tbody>
</table>

CSF: Cerebrospinal fluid; VATS: Video-assisted thoracoscopic surgery; ND: No data.

wound (Figure 2). The thoracic spinal neurofibroma had been almost totally removed but was complicated with pneumothorax, cerebrospinal fluid (CSF) leakage, and TP.

**Histological examination**

The tumor was pathologically proven to be a neurogenic tumor consisting of neurofibroma (Figure 3). According to the postoperative microscopic examination, the cyst contained chronic inflammation of tissue and no residual tumor.

**FINAL DIAGNOSIS**

The presented case was diagnosed with tension pneumocephalus after a thoracoscopic resection to remove a neurogenic tumor.

**TREATMENT**

He then was admitted to the intensive care unit for further close monitoring and medical treatments including full hydration, prophylactic antibiotics use, O₂ supplementation, lying absolutely flat, and primary suturing and debridement of the chest...
Histological examination of the spinal tumor. A: Intraoperative image of the posterior mediastinal tumor demonstrated well-defined border, which was pathologically proved to be neurogenic tumor; B-F: A histological image of the neurofibroma showing bland spindle cells with wavy nuclei and pale eosinophilic cytoplasm (scale bar 50 μm) (B), secondary degeneration of hyalinization (scale bar 200 μm) (C), calcification (scale bar 100 μm) (D), cyst (scale bar 500 μm) (E), and hemorrhage (scale bar 200 μm) (F).

wound. However, the symptoms did not improve. Thus, surgical treatments were performed to repair the CSF leakages. Following a left T2-3 hemilaminectomy and costotransversectomy, a cystic meningocele was found. After the cyst pouch was totally removed, the previous remnant tumor stump and surgical clip were explored meticulously. CSF leaking from the surgical clip near the dura was disclosed. The leakage site was wrapped with autologous fat, gelfoam, tissue glue, and duraseal in a layer-by-layer manner (Figure 4). Finally, the wound was closed in a layer-by-layer manner with a Jackson-Pratt tube that was left in the surgical field.

OUTCOME AND FOLLOW-UP

At the 2-wk follow-up and evaluation, the patient denied experiencing any further headaches. The follow-up brain computed tomography scan showed resolution of the pneumocephalus, pneumoventricle, pneumothorax, and pneumospine (Figure 5).

DISCUSSION

The reported theories of pneumocephalus development include the “ball-valve theory” and “inverted soda bottle effect”[13,14]. The possible mechanisms to develop pneumocephalus after thoracoscopic resection include dural tearing with persistent cerebrospinal fluid leakage, such that air can gain access from the leakage site to the intradural space and reach the cranial cavity. The negative pressure produced by chest tube suction can even deteriorate the CSF extravasation. On the other hand, an upright head position also allows the air to easily enter the intradural space from the leakage site. Relatedly, in our case, a poorly healing thoracoscopic access wound resulted in pneumothorax and an aggravating pneumocephalus. Based on the imaging results of the current case, TP was indicated by two imaging characteristics. One, the “Mt. Fuji sign,” means that subdural air with increased tension is separating and compressing the bilateral frontal lobes and widening the interhemispheric space, such that the
resulting image resembles the silhouette of Mt. Fuji. The other, the “air bubble sign,” indicates that multiple air bubbles are scattered through the cistern, with these air bubbles putatively entering the subarachnoid space due to tearing of the arachnoid membrane caused by increased tension in the subdural space[2,3]. This appeared to apply in our case, with the source of intracranial air being a spinal dural defect that resulted in air also being apparent in the spinal cord, ventricle, and basal cistern[12].

We performed the literature review using a search of English literature from PubMed, in which the source of databases ranged from 2000 to 2019. The key words and criteria for search engine was represented as “pneumocephalus [title] AND spinal tumor” where 11 results were generated. We further summarized the reported cases in which pneumocephalus developed after surgical treatments for spinal or posterior mediastinal tumor and specified their subsequent interventions (Tables 1, 2). Though only 23 cases in which pneumocephalus developed after surgical treatments for spinal or posterior mediastinal tumor had been reported within the recent 10 years, most patients can be treated only by conservative medical therapeutic strategies, including
highly concentrated O₂ supplementation to accelerate the resorption of intracranial air, bed rest with the head laid flat to minimize CSF leakage from the dural defect, avoidance of the Valsalva maneuver, and prophylactic antibiotics use if meningitis is highly suspected (Tables 1, 2). Surgical intervention consisting of the evacuation of the intracranial air and repair of the dural defect is indicated when the above conservative treatments fail, when the recurrence of pneumocephalus occurs, or when there are signs of increasing intracranial pressure[1-4,12]. In our case for progressive pneumocephalus, we preferred to conduct surgical intervention rather than conservative treatment. The direct method of dura repair was chosen in consideration to the developing CSF fistula. Then, the intracranial air was evacuated until the CSF leakage site was sealed completely. Initial frontal burr hole decompression for pneumocephalus was demonstrated in a similar case for rapid consciousness change and cranial nerve palsy under the impression of increased intracranial pressure signs, of which the clinical signs were improved postoperatively[12]. In our opinion, the direct method for dural repair can obliterate the origin of CSF leakage and fistula formation. Thus, the pneumocephalus may be absorbed spontaneously as long as there is no further air getting access[13].

Intraoperative primary repair with suturing is highly recommended for preventing postoperative CSF leakage[16]. However, the primary closure of a durotomy may be difficult because of its location (e.g., in the case of ventral or far-lateral durotomies), a large dural defect, poor tensile strength of the dura, or a minimal invasive wound limiting the exposure and access[15]. Several alternative methods of durotomy repair have been described. For example, an additional dorsal durotomy for far-lateral or dorsal defects can allow such defects to be more easily visualized and plugged with autograft or suturing[15], while autograft coverage with dural sealant in cases of durotomies that cannot be repaired primarily due to limited visibility or access[15,17], an aneurysm clip, or a titanium clip have also been reported[18,19]. In our case, as the CSF leakage might have derived from the previous endoscopically clipped tumor stump near the dural sac at the T3 level, such that it would have been difficult to perform a primary suture repair. Thus, we plugged and wrapped the stump with an autograft of fat, tissue glue, gelfoam, and duraseal (Figure 4).

**CONCLUSION**

The risk of getting a pneumocephalus after thoracoscopic resection of a spinal tumor cannot be neglected since the intraoperative repair is hard to access. The direct approach for dural repair may be an attemptable way to eliminate the CSF leakages.

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Accelerated Infliximab Induction for Severe Lower Gastrointestinal Bleeding in a Young Patient with Crohn’s Disease: A Case Report

Jing Zeng, Feng Shen, Jian-Gao Fan, Wen-Song Ge

Abstract

BACKGROUND
Severe lower gastrointestinal bleeding (SLGIB) is a rare complication of Crohn’s disease (CD). The treatment of these patients is a clinical challenge. Monoclonal anti-TNFα antibody (IFX) can induce relatively fast mucosal healing. It has been reported for the treatment of SLGIB, but there are few reports on accelerated IFX induction in CD patients with SLGIB.

CASE SUMMARY
A 16-year-old boy with a history of recurrent oral ulcers for nearly 1 year presented to the Gastroenterology Department of our hospital complaining of recurrent periumbilical pain for more than 1 mo and having bloody stool 4 times within 2 wk. Colonoscopy showed multiple areas of inflammation of the colon and a sigmoid colon ulcer with active bleeding. Hemostasis was immediately performed under endoscopy. The physical examination of the patient showed scattered small ulcers in the lower lip of the mouth and small cracks in the perianal area. Combined with his medical history, physical examination, laboratory examinations with high C-reactive protein (CRP), platelet count (PLT), erythrocyte sedimentation rate (ESR) and fecal calprotectin levels, imaging examinations and pathology, a diagnosis of CD was taken into consideration. According to the pediatric CD activity index 47.5, methylprednisolone (40 mg QD) was given intravenously. The abdominal pain disappeared, and CRP, PLT, and ESR levels decreased significantly after the treatment. Unfortunately, he had a large amount of bloody stool again after 1 wk of methylprednisolone treatment, and his hemoglobin level decreased quickly. Although infliximab (IFX) (5 mg/kg) was given as a combination therapy regimen, he still had bloody stool with his hemoglobin level decreasing from 112 g/L to 80 g/L in a short time, so-called SLGIB. With informed consent, accelerated IFX (5 mg/kg) induction was given 7 days after initial presentation. The bleeding then stopped. Eight weeks after the treatment, repeat colonoscopy showed mucosal healing; thus far, no recurrent
Core Tip: Severe lower gastrointestinal bleeding (SLGIB) is a rare complication of Crohn's disease (CD) that is potentially life-threatening. The treatment of these patients is a clinical challenge. Monoclonal anti-TNFα antibody infliximab (IFX) can induce relatively fast mucosal healing. It has been reported for the treatment of SLGIB, but there are few reports on accelerated IFX induction in CD patients with SLGIB. We present a patient with CD complicated with SLGIB. The bleeding was finally controlled, and colonoscopy showed mucosal healing after accelerated IFX induction.

INTRODUCTION
Crohn's disease (CD) is a subtype of inflammatory bowel disease (IBD)[1]. Severe lower gastrointestinal bleeding (SLGIB) is an uncommon but potentially life-threatening complication of CD. The incidence of acute LGIB secondary to CD in China ranges from 0.6% to 6%[2]. The definition of SLGIB in CD has changed over the years. In 1976, Homan et al[3] defined it as profuse rectal bleeding that required blood transfusions to maintain normal vital signs. In a recent case series, the definition was again modified to a drop in hemoglobin (Hb) of 2 g/dL below the baseline +/-hemodynamic instability or an abrupt fall in Hb to less than 9[4,5]. Monoclonal anti-tumor necrosis factor (TNF)-α antibody (IFX) can induce relatively fast mucosal healing. It has been reported for the treatment of SLGIB, but there are few reports on the accelerated IFX induction in CD patients with SLGIB. We present a patient with CD complicated with SLGIB. The bleeding was controlled, and colonoscopy showed mucosal healing after accelerated IFX induction.

CASE PRESENTATION

Imaging examinations
Initial colonoscopy on 15 July 2020 revealed multiple areas of inflammation of the colon (Figure 1A) and a sigmoid colon ulcer with bleeding (Figure 1B). Hemostasis was achieved under endoscopy (Figure 1C). Enhanced computerized tomography of the small intestine noted thickened walls of the small intestine and colon on 18 July 2020 (Figures 2A, 2B). Pathology revealed acute on chronic inflammation with granulation tissue, compatible with CD. In addition, Cytomegalovirus (CMV) immunohistochemical staining and acid-fast staining were negative (Figures 3A, 3B). Colonoscopy on 25 July 2020 showed multiple ulcers with hemorrhage (Figures 4A, 4B). After accelerated IFX induction therapy, colonoscopy showed mucosal healing in 8 wk (Figures 5A, 5B).

Laboratory examinations
Blood analysis revealed leukocytosis (16.67 × 10⁹/L), with predominant neutrophils
(82%), mild anemia (hemoglobin 11.3 g/dL), and platelets that were increased slightly to $348.0 \times 10^9$/L. Serum C-reactive protein content was increased at 123 mg/L (normal range < 5 mg/L), and the red blood cell sedimentation rate was 82 mm/h. The fecal calprotectin was increased at 1703.43 µg/g, and both anti-intestinal goblet cell and anti-pancreatic exocrine gland antibodies were positive. Prothrombin and partial thromboplastin time, electrocardiogram and urinalysis were all normal. CMV immunoglobulin (Ig) M, IgG, CMV DNA, Epstein-Barr virus (EBV)-VCA IgM, EBV DNA, human immunodeficiency virus (HIV) antibody (Ab), amoeba antibodies, Clostridium difficile toxin, Salmonella, Shigella cultures, and Campylobacter were all negative. Positive stool pus and occult blood were noted.

Figure 1 Endoscopic findings (15 July 2020). A: Multiple inflammation of the colon; B: Sigmoid colon ulcer with bleeding; C: Hemostasis under endoscopy.

Figure 2 Computed tomography (18 July 2020). A: Thickened walls of the small intestine; B: Thickened walls of colon.

Figure 3 Pathology. A: Acute on chronic inflammation with granulation tissue, consistent with Crohn’s disease; B: Cytomegalovirus immunohistochemical staining and acid-fast staining were negative.
Figure 4 Endoscopic findings (25 July 2020). A, B: Multiple ulcers with hemorrhage.

Figure 5 Endoscopic findings (8 wk after accelerated IFX induction). A, B: Eight weeks after accelerated IFX induction therapy, colonoscopy showed mucosal healing. IFX: Anti-TNFα antibody.

Physical examination
Physical examination on admission showed a body temperature of 36.0 °C, heart rate of 91 bpm, arterial blood pressure of 113/66 mmHg, respiratory rate of 18/min, and oxygen saturation in room air of 100%. Small ulcers could be seen in the mouth and scattered on the lower lip, and small cracks could be seen around the anus.

Personal and family history
The patient had a noncontributory previous personal and family history.

History of past illness
He had a history of recurrent oral ulcers for nearly 1 year without special treatment.

History of present illness
The patient complained of recurrent periumbilical pain for more than 1 mo with no obvious causes. Appendicitis was suspected in the local hospital, and he received anti-inflammatory treatment. However, the periumbilical pain did not improve, and he suffered bloody stool 4 times in the 2 wk before admission. He also mentioned weight loss of 10 kg within 1 year.

Chief complaints
A 16-year-old boy presented to the Department of Gastroenterology in our hospital complaining of recurrent periumbilical pain without obvious predisposing causes for more than 1 mo and bloody stool 4 times within 2 wk.

FINAL DIAGNOSIS
The final diagnosis of the presented case was SLGIB secondary to CD (Montreal A1L2B1p). The pediatric CD activity index (PCDAI) was 47.5 points.
TREATMENT

The patient, following the diagnosis of severe CD, was immediately started on methylprednisolone 40 mg QD intravenously combined with nasal feeding enteral nutrition support treatment. IFX (5 mg/kg) was given when uncontrolled bleeding occurred 1 wk after treatment with methylprednisolone on 25 July 2020. The second IFX (5 mg/kg) treatment was given on 1 August 2020 for uncontrolled SLGIB. After 8 wk of treatment, colonoscopy showed mucosal healing.

OUTCOME AND FOLLOW-UP

On 29 September 2020, follow-up colonoscopy showed that the mucosa had healed without any ulcers (Figures 5A, 5B). After 8 wk of IFX treatment, the PCDAI was 5 points. Thus far, the bleeding has not recurred. His body weight increased 10 kg, and his height increased 2 cm as of 1 August 2021. The timeline information of this patient was shown in Figure 6.

DISCUSSION

CD is a subtype of IBD, which is characterized by transmural inflammation of the entire intestinal wall, which can lead to various serious complications, including intestinal obstruction, intra-abdominal abscess and intestinal fistula[1]. Among them, SLGIB is an uncommon but potentially life-threatening complication of CD. Cirocco et al[6] reported that the incidence of lower gastrointestinal bleeding (LGIB) in 631 CD patients was 0.6%, while Kim et al[4] reported that the incidence of LGIB in 1731 CD patients was 4%. In general, the reported incidence of acute LGIB secondary to CD in China ranges from 0.6% to 6% [2,4,7]. Li et al[1] also found that patients with a past medical history of bleeding, lesions involving the left colon, and the use of azathioprine for less than 1 year were all risk factors for acute LGIB in CD patients. Male sex was also found to be a risk factor[8]. Mazor et al[9] and Severs et al[10] even reported that only male sex was independently associated with complex complications, including stenosis, penetrating lesions and perianal lesions, and a high risk of needing surgical intervention. In our case, the patient was a 16-year-old boy. Therefore, further research may be needed to confirm the influence of sex on acute LGIB in CD patients in the future.

The treatment of CD has developed continuously in recent years, including the use of mesalazine, corticosteroids, and immunosuppressants. For SLGIB in CD patients, surgical treatment was the most commonly chosen treatment strategy in the past; it has a lower rebleeding risk than conservative drug therapy [1,11]. However, it was also very difficult to identify the bleeding sites accurately in SLGIB in CD, and the risk of postoperative intestinal obstruction, anastomotic leakage, fistula, and short bowel syndrome was very high[12]. In our case, the patient was very young. Considering the large range of lesions and possible postoperative complications, surgical intervention was not considered. In some SLGIB in CD, local injection of adrenaline or thrombin under endoscopy could effectively stop the bleeding[13]. However, it is difficult to stop the bleeding under endoscopy if there are multiple bleeding sites with both ileum and colon involvement. In this case, we performed endoscopic homeostasis twice but were unable to stop the bleeding completely. Belaiche et al[13] found that corticosteroids could be used to treat LGIB in CD patients. However, some studies[4,14,15] reported that the effect of corticosteroids on the treatment of LGIB in CD was not exact and that those receiving corticosteroids were more likely to rebleed. The patient in our case was treated with standard corticosteroid therapy at first, but he still had bloody stool after 1 wk of treatment.

With the advent of IFX, an increasing number of reports have described IFX for the treatment of CD with acute LGIB with a significant effect. IFX is an anti-TNFα monoclonal antibody that can counteract the TNF-α-mediated intestinal inflammatory response, quickly reduce inflammation of the intestinal wall, promote ulcer healing, and effectively prevent and control the occurrence of bleeding[11]. As early as 2003, Papi et al[16] reported 2 cases of CD patients with recurrent LGIB that achieved mucosal healing after the application of IFX (5 mg/kg), and bleeding did not reoccur. Aniwon et al[11] also reported 7 cases of LGIB secondary to CD. All patients stopped bleeding after 1–2 rounds of treatment with IFX (5 mg/kg). Therefore, IFX may be an ideal choice for LGIB in CD.
Nevertheless, there were a large number of patients who did not have a good response to IFX, which might be related to a high drug clearance rate, excessive stool loss, reduced drug exposure, and poor drug response\cite{17,18}. For these patients, some studies suggested shortening the IFX infusion time from the recommended 2 h to 1 h to improve the therapeutic effect\cite{19}. On the other hand, accelerated IFX induction is increasingly used in moderate to severe ulcerative colitis (UC) patients who do not have a good response to the first IFX induction. In the guidelines, the "accelerated IFX induction (AD IFX)" is when the frequency of administration of IFX during the induction period exceeds the frequency of administration recommended in the latest product monograph\cite{20}. AD IFX can better and more quickly control the disease\cite{21}. It can reduce the occurrence of early colectomy\cite{22}. The decision to use shorter dosing intervals rather than dose escalations is based on the pharmacokinetics of IFX. Therefore, AD IFX has been increasingly used in clinical practice. Since 2014, AD IFX induction in accelerated severe UC patients has been used in clinical practice in the Republic of Ireland, specifically for patients with more severe disease or poor initial response to standard treatment of IFX\cite{21}. However, AD IFX is rarely reported to be used in CD patients. In our case, according to the PCDAI, methylprednisolone (40 mg QD) was given intravenously. Unfortunately, he had a large amount of bloody stool again after 1 wk of methylprednisolone treatment, with a rapidly decreasing hemoglobin level. Although IFX (5 mg/kg) was given as a combination therapy regimen, he still had bloody stool, with the hemoglobin level decreasing sharply in a short time as in SLGIB. With informed consent, AD IFX (5 mg/kg) was given 7 days after the first treatment. The bleeding then stopped. Eight weeks after the treatment, colonoscopy showed mucosal healing, the patient was symptom-free, and thus far, no recurrent bleeding has occurred. However, it is worth noting that although Peyrin-Biroulet et al\cite{23} found that IFX did not increase the risk of death, tumor or serious infection in CD patients through meta-analysis, a clinical study\cite{24} found that the incidence of upper respiratory tract and urinary tract infections in the IFX group and the control group were 36% and 26%, respectively. There was also a case report of a fatal pulmonary disease caused by IFX\cite{25}. However, in our patient, we have not observed adverse side effects in the follow-up to date.

CONCLUSION

SLGIB is an uncommon but potentially life-threatening complication of CD. It is suggested that AD IFX may be an effective treatment option if the bleeding is severe and cannot be well controlled in these patients. However, in view of the limited medical evidence at present, it is necessary to carefully identify the applicable populations systematically and actively summarize the applicability in such populations. It is necessary to conduct larger-scale, multicenter, prospective studies to further decide whether AD IFX is advantageous.
REFERENCES


Occupational fibrotic hypersensitivity pneumonia in a halogen dishes manufacturer: A case report

Min Wang, Hao-Hui Fang, Zi-Feng Jiang, Wei Ye, Rong-Yu Liu

ORCID number: Min Wang 0000-0002-5497-288X; Hao-Hui Fang 0000-0003-1975-282X; Zi-Feng Jiang 0000-0003-4185-3889; Wei Ye 0000-0001-6404-7156; Rong-Yu Liu 0000-0002-0483-0808.

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Abstract

BACKGROUND
Fibrotic hypersensitivity pneumonitis (FHP) is an allergic and diffuse pneumonia caused by repeated inhalation of antigenic substances, and sometimes developed in people working in specific environments. While novel antigens and exposures continued to be described, physicians should maintain a high suspicion of potential exposures. A detailed assessment of the patient's occupational exposures as well as living environment is necessary and complete allergen avoidance is the first and most important step in the management of FHP once the allergens are determined.

CASE SUMMARY
A 35-year-old female was admitted to the hospital with a cough and breathing difficulties for more than one year. She was a nonsmoker and a manufacturer of halogen dishes, which are characteristic Chinese foods, for 15 years without any protection. High resolution computed tomography of the chest demonstrated an interstitial pneumonia pattern. Pulmonary function examination showed restricted ventilation dysfunction and a significant reduction in dispersion ability. Cell differentiation in bronchoalveolar lavage fluid demonstrated lymphocytosis (70.4%) with an increased lymphocyte CD4/CD8 ratio (0.94). Transbronchial lung biopsy combined with lung puncture pathology showed diffuse uniform alveolar interval thickening, chronic inflammatory cell infiltration, a proliferation of tissue in the bronchial wall fiber and alveolar epithelial follicle degeneration, resulting in fibrosis.

CONCLUSION
Exposure to spices used for the production of halogen dishes may cause FHP.

**Key Words:** Halogen dishes; Inhalation; Interstitial pneumonia; Spices; Fibrotic hypersensitivity pneumonitis; Case report

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**Core Tip:** Fibrotic hypersensitivity pneumonitis (FHP) is a disease related to immunological response to an inhaled antigen. Avoiding contact with susceptible antigen is the key. Here, we report a case of FHP in a halogen dishes manufacturer probably associated with exposure to the spices. We recommend to enhance respiratory protection during the production of such dishes to prevent this lung disease.

**INTRODUCTION**

Fibrotic hypersensitivity pneumonitis (FHP) is a chronic and fibrosing interstitial lung disease caused by inhaled antigen exposure which can develop in people working in specific environments or with specific career[1]. The commonly known form is Farmer's lung[2]. Halogen dishes are Chinese cuisines in which long-term boiling of various spices powder is required before meat and vegetables are added. Each halogen maker has a so-called secret recipe, but almost all contain ginger, pepper, soy sauce, and other spices. A single case of hypersensitivity pneumonitis (HP) associated with curry powder and ground pepper in a potato chip factory has been described[3]. We herein report a case of FHP in a halogen dishes manufacturer, which may have been caused by the inhalation of spices.

FHP can lead to impaired respiratory function, reduced disease-related quality of life, and early mortality. Management of FHP should start with exposure remediation once the source of allergy is identified. A high index of suspicion is important to diagnosis, even after innocuous and apparently trivial exposures to potential antigens. We herein report a case of FHP in a halogen dishes manufacturer, which may have been caused by inhalation of spices.

**CASE PRESENTATION**

**Imaging examinations**

High resolution computed tomography (HRCT) of the chest showed thickening of interlobular septa and central lobular nodules which revealed honeycomb changes in severe areas (mainly in the lung base), as well as traction bronchiectasis (Figure 1).

**Laboratory examinations**

Routine blood, liver function, renal function tests and serum sodium, potassium, creatinine, magnesium, and calcium were all within normal limits. Blood tumor biomarkers including anti-nuclear antibody, anti-centromere antibody, anti-neutrophil cytoplasmic antibody, and Scl-70 antibody screens and C-reactive protein were negative. Pulmonary function tests showed a forced vital capacity (FVC) of 1.75 L (51.2% predicted), a forced expiratory volume in 1 s (FEV1) of 1.63 L (55%), an FEV1/FVC ratio of 109.6%, and carbon monoxide diffusing capacity 11.9 mmHg/mL/min (39% predicted). Cytology of bronchoalveolar lavage (BAL) fluid showed a large number of lymphocytes (the total number of cells was 4.16x10^6/mL, lymphocytes accounted for 70.4%, of which the lymphocyte CD4/CD8 ratio was 0.94, and bronchoscopy was performed to rule out a superimposed infection. Allergen
Figure 1 Chest high-resolution computed tomography (HRCT) images. A-C: showing traction bronchiectasis and extensive fibrosis, reticular changes (especially in the outer lung band and the double lower lung); D-F: showing the corresponding mediastinal window.

determination showed that tree, pollen, ragweed, Artemisia argyi, home dust mite, home dust, cat hair, dog hair, cockroach, mold combination, legume, egg white, milk, peanut, soybean, beef, mutton, cod, shrimp, crab, salmon, lobster, scallop, etc. were all negative.

Physical examination
On examination, her temperature was 36.7 °C, blood pressure was 118/82 mmHg, heart rate was 74 bpm, oxygen saturation was 92% in room air, and respiratory rate was 22 breaths/min. The patient was identified as Grade 3-shortness of breath according to the mMRC (Modified Medical Research Council) dyspnea scale and lung examination revealed bilateral Velcro like crackles in the lower lung fields. The rest of her physical examination was unremarkable.

Personal and family history
This patient had no special personal and family history.

History of past illness
She was a self-employed worker, cooking and selling halogen dishes for over 15 years, without any measures to protect the respiratory tract. There was no history of orthopnea, chest pain, or paroxysmal nocturnal dyspnea. She denied smoking and there was no history of asthma, allergies, or any other prior pulmonary disease.
**History of present illness**
The patient took anti-inflammatory and cough medications intermittently, but there was no improvement in her symptoms.

**Chief complaints**
A 35-year-old Chinese woman with no significant medical history was admitted to our hospital because of a cough and breathing difficulties. She was a self-employed cook who produced and sold halogen dishes for more than 15 years without appropriate equipment to protect the airway from inhalation.

**MULTIDISCIPLINARY EXPERT CONSULTATION**
Fan-Qing Meng, MD, Professor, Department of Pathology. Fibrin-like exudation, more lymphocytes, foam-like tissue cells and a small number of macrophages were observed on histopathology of lavage fluid, suggesting persistent exposure to inhaled antigen. Transbronchial lung biopsy (TBLB) and computerized tomography-guided percutaneous lung puncture showed chronic lymphocyte and foamy macrophages infiltration, diffuse, relatively uniform alveolar septal thickness, hyperplasia of fibrous tissue in the bronchial wall, resulting in fibrosis (Figure 2).

**FINAL DIAGNOSIS**
Occupational FHP due to probable long-term exposure of spices in a halogen dishes manufacturer.

**TREATMENT**
The patient was started on prednisone 30 mg/d and pirfenidone anti-fibrosis treatment. Considering the side effects of high doses of hormones, the patient was discharged on a tapering schedule of prednisolone which was reduced by 5 mg every 2 wk.

**OUTCOME AND FOLLOW-UP**
The main symptoms of cough and breathing difficulties gradually improved slightly three months later, but no improvement in chest HRCT was noted. No significant adverse side-effects were noticed. The patient is currently on the lung transplant list.

**DISCUSSION**
This patient met the diagnostic criteria for FHP as she had a cough, breathing difficulties, long-term inhalation of spices, lymphocytic cellular pattern on BAL, bibasilar rales, reduction in diffusion capacity, and compatible radiologic and histopathological findings. BAL can not only exclude other major causes of interstitial pneumonia including alveolar hemorrhage, malignancy, infection, and eosinophilic lung disease, but also exclude common allergens. While BAL lymphocyte percentage in HP can vary substantially from 1.7% to 82%[4], in this patient BAL showed an obvious lymphocytic cellular pattern (70.4% lymphocytes) defined as a BAL differential count greater than 15%[5]. Additionally, aggregation of foamy macrophages and lymphocyte infiltration was observed which indicated exposure to inhalant pathogens [6]. Serologic studies for spices were not performed due to the patient’s insurance status (she only had basic medical insurance and restricted economics), and had no relevance to the diagnosis even if negative as this would not exclude the clinical diagnosis of HP due to exposure to spices. Therefore, inhaled spices were the presumed cause of FHP in this case, especially given the absence of any other identifiable exposures.
Novel antigens and exposures related to occupation continue to be described, even innocuous and trivial exposures to potential antigens such as green tea\(^7\), citrus\(^8\), and pyrethrin\(^9\) have been described. To our knowledge, this is the first case of FHP in a halogen dishes manufacturer caused by spices globally, which was confirmed by the presence of fibrosis through histological evaluation of TBLB and percutaneous lung puncture. However, it has also been pointed out that in the presence of a concomitant allergic predisposition, such as bronchial asthma, allergic rhinitis, or chronic bronchitis, the biological response to inhalation may be enhanced. There was no apparent comorbidity in our patient and she was a nonsmoker.

Heightened awareness of potential exposures is imperative in making a diagnosis and a detailed assessment of occupational exposures as well as the occupational environment is necessary as demonstrated in this case. Avoiding contact is the key for patients with HP, not only for patients but also for other individuals who may be exposed to the same allergen\(^9\). Although there are no obvious symptoms or failure of regular occupational disease physical examination or disease detection, it is essential to remind workers of their safety during the production process\(^8\) (respirator, masks, improve ventilation, regular monitoring of air quality) and the compliance of workers should be confirmed. For those with established allergies, there are various ways to avoid exposure, for example, by changing jobs or occupations. Clinically appreciable improvement in symptomatic, physiologic, and radiographic features may be seen only in patients with non-fibrotic HP\(^10\). Due to the long and insidious exposure to antigen, fibrosis was observed both radiologically and pathologically in our patient. Management of FHP should start with exposure remediation where possible, oral glucocorticoids and azathioprine achieved an initial improvement in pulmonary function tests and symptoms\(^11\), anti-fibrosis therapy should be considered in patients with symptomatic or progressive disease, and non-pharmacologic and supportive management should be offered and, in cases of treatment-resistant, progressive illness, lung transplant should be considered\(^12,13\). Based on this, we advised our patient to change her occupation, and prednisone and anti-fibrosis therapy was given to improve her symptoms. Halogen dishes manufacture is mostly a family business in China, the patient inherited the shop from her mother and had no other life skills, although she was no longer responsible for food preparation, she still sold the halogen dishes at the counter. Following treatment, her symptoms improved slightly and requiring long-term oxygen therapy, the HRCT scan showed no...
improvement. The patient is currently on the waiting list for a lung transplant.

**CONCLUSION**

Attention should be paid to the possibility of inhalation hypersensitivity pneumonitis caused by spices. Improvements in respiratory protection measures should be suggested for workers during the production process to avoid this type of lung disease.

**REFERENCES**


Using a fretsaw in treating chronic penial incarceration: A case report

Yi Zhao, Xiao-Qiang Xue, Hou-Feng Huang, Yi Xie, Zhi-Gang Ji, Xin-Rong Fan

Abstract

BACKGROUND
Penial incarceration (PI) is a rare situation. It is usually caused by a foreign object which strangles at the base of the penis. PI may derive from pranks, sexual demand, mental disease, or intention to prohibit urinary disease. Generally, these situations are emergent and immediate treatments are needed. Cases of chronic PI are less reported, and their treating methods are yet to be discussed.

CASE SUMMARY
We reported a case on treating a 73-year-old male who had PI with a metallic hoop for three months. After multidisciplinary consultation, the operation was performed successfully with the help of a fretsaw. Despite the chronic strangulation, the prognosis of the patient was satisfying. To the best of our knowledge, this case was rare and precious as it featured the longest strangulating time, which might enlighten the treating process of future PI cases. Also, we have reviewed and summarized major published cases to encapsulate appropriate approaches when facing diverse strangulation situations.

CONCLUSION
The selection of surgical tools depends on the material of the strangulating objects, the availability of equipment, and the severity of the penial damage. The urination function may not be affected after three months of incarceration as in our case, whilst prudent preoperative measures and multidisciplinary evaluations are always essential. Although using a fretsaw is comparatively slow, it is safe and feasible to treat metallic penial incarceration.

Key Words: Penial incarceration; Chronic penial strangulation; Fretsaw; Surgical treatment; Literature review; Case report
Core Tip: Penial incarceration (PI) is a rare clinical situation. We report a case of chronic PI, where a multidisciplinary task force was established for surgical strategy planning. We adopted the orthopedic fretsaw to split the metallic hoop. The patient reported no complications one year after the surgery. As the treatment of PI has not been summarized yet, we also performed a mini review of the literature regarding the treating approaches under certain circumstances. This case was unique because it featured the longest reported strangulating time, and it offered some first-hand experience on treating chronic penial incarceration.

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INTRODUCTION
Penial incarceration (PI) is a rare clinical situation that was firstly reported in 1755[1]. It is usually caused by a foreign object that strangulates at the base of the penis[2]. PI may derive from pranks, sexual demand, mental disease, or intention to prohibit urinary disease[1]. In most cases, the strangulating objects would block venous and arterial blood supply and result in ischemic necrosis. Hence, PI usually requires immediate intervention to save the penis function[1,3]. Depending on the material and hardness, strangulating objects can be either metallic or non-metallic[4]. Studies report that PI is usually caused by non-metallic foreign objects in younger patients, such as hair and rubber bands. In contrast, in elderly patients, metallic foreign objects are more likely to be found[5].

Herein, we report a rare case of a patient with chronic PI for three months. The strangulation was treated by operation successfully, and the patient’s penial function was not affected. Published approaches on evaluating and treating PI are reviewed, and our experience on this case is shared.

CASE PRESENTATION
Imaging examinations
No specific imaging examination was taken for diagnostic purposes as the diagnosis was not ambiguous.

Laboratory examinations
Nothing abnormal was shown in the laboratory examinations.

Physical examination
Physical examination demonstrated a swollen penis at the distal end of the metallic ring, no skin necrosis or numbness was reported, nor stinky odor was smelt. This copper hoop was 40 mm in the external diameter, with a 10 mm width and a 2 mm thickness (Figure 1).

A close physical examination found that the metallic hoop could be rotated slightly at the incarceration location. However, it could not be removed directly whatsoever. The patient's vital sign was stable.

Personal and family history
The patient had no markable personal and family history.

History of past illness
The patient reported multiple comorbidities, including diabetes, high blood pressure (up to 190/110 mmHg), and coronary heart disease with four stents implanted. The patient took aspirin and clopidogrel routinely for secondary prevention purposes.
Zhao Y et al. Fretsaw treating chronic penial incarceration

Figure 1 Preoperative view of the penis.

History of present illness
The patient reported that he "accidentally" put the copper hoop in his penis three months ago, and it was challenging to be taken off. As there was no acute pain, bleeding, or any other uncomfortable symptoms at that moment, he decided to do the self-observation rather than visit the emergency department. During his observation period, he found that his penis gradually became swollen, and thereafter the urination gradually became arduous. After three-mo-long consideration, he decided to visit the outpatient department of our medical center on his own.

Chief complaints
A 73-year-old man visited the outpatient department of our hospital with a copper hoop strangulating around the base of his penis.

MULTIDISCIPLINARY EXPERT CONSULTATION
Aspirin and clopidogrel had been ceased seven days before the operation. Both the cardiology department and anesthesia department regarded the risk to anesthesia as acceptable for surgery. Firefighters stated that they had no experience in handling such cases.

Dentists suggested that the fixed dental drill might be an alternative, as they had previously tested its efficiency and feasibility on a stainless-steel nut. It could cut a 1 mm deep gap on the nut within 25 s, let alone the softer copper hoop in this case. However, since the head of the dental drill was easily destructed, this plan was eventually abandoned.

Considering the familiarity with available equipment in the operating room, we also invited several scrubbing nurses for surgical instrument preparation. The fretsaw, which had been commonly used in the field of orthopedics and neurosurgery, was recommended.

FINAL DIAGNOSIS
The final diagnosis of the presented case is chronic PI with a metallic hoop.

TREATMENT
We wrapped the distal penis with a bandage preoperatively to alleviate regional edema and placed a thin catheter between the penis and the hoop as a retraction. The catheter was pulled out intraoperatively, and then a condom was cautiously placed. Nevertheless, because of the edema of the prepuce, we failed to take the hoop off by hand, even with lubrication.
Therefore, penile aspiration was performed to reduce the edema. Meanwhile, we exploited a pincher to fix the hoop, an intestinal spatula to protect the underlying skin, as well as sterile water for cooling secondary heat damage. A video clip of the surgical procedure could be found online as the Supplementary Material. The foreign object was finally removed after 100 min of fretsaw cutting (Figure 2). There was scarcely any bleeding during the surgery. A urinary catheter was indwelled in case of temporary dysuria. The catheter was withdrawn and the patient was discharged in good condition two days after surgery.

OUTCOME AND FOLLOW-UP

There were no complications like dysuria, erectile dysfunction, urinary irritation, or urethral fistula through telephone follow-up on the exact time of one month and one year after surgery.

DISCUSSION

PI is an urgent situation. If treated untimely, it can result in devastating consequences, as the persistent constriction might lead to genital vascular occlusion, further causing skin loss, urethral-cutaneous fistula, erectile dysfunction, and even penile loss[6]. Given that no particular tool has been designed for relieving the strangulation, and occasionally the patient is too old with severe comorbidities, a multidisciplinary team, sometimes including firefighters, physicians, and scrubbing nurses, is suggested to be established.

Albeit cases of penial strangulation and its treatments had been sporadically reported, there are no universal treating protocols due to the differences in patients’ status, strangulating objects, and medical conditions. Various objects could induce the strangulation of the penis. Based on the material, they could be roughly classified as metallic and non-metallic[7]. Trivedi et al[3] suggested that the duration of incarceration was an essential factor affecting the prognosis. Namely, suppose the penile strangulation cannot be relieved in time, it may lead to irreversible ischemic necrosis, gangrene of the penis, even penile self-amputation, urethral fistula, and penile erectile dysfunction.

As far as we are concerned, the penis injury can be divided into different grades, varying from edema, skin loss, urethral fistula to complete amputation[8], that is: Grade 1: simple distal prepuce edema without penile skin ulcer or urethral injury; Grade 2: skin injury and cavernous compression, penile prepuce edema, accompanied by decreased sensation, but no urethral injury; Grade 3: urethral injury, loss of distal penile sensation, but no urinary fistula; Grade 4: the rupture of the cavernous urethral body and result in urinary fistula, further compression of the penile cavernous body with loss of sensation; and Grade 5: necrosis or spontaneous disconnection of the distal end of the penis. In our experience, anti-infection and decompression are basic principles to deal with such cases. At the same time, the severity of strangulation is mainly related to the foreign object itself, such as hardness, size, and smoothness. More specifically, when the surface between the incarcerating object and the penis is not smooth or too tight, the penis would present acute edema, ulcer, and even necrosis. However, long-term strangulation may only cause edema of the prepuce and local skin superficial ulcer when the incarceration is not severe, rather than penial necrosis and urinary fistula. This situation might be partial because, at this time, penial and urethral cavernous bodies are shielded from edematous skins.

Generally, the treatment attempts we take should minimize the trauma to local tissues[9]. Applying lubricating oil with appropriate traction to remove foreign objects directly is preferred. For those with severe incarceration and noticeable swelling, penis piercing could be performed. The piercing sites could be either the edematous skin, the subcutaneous skin, or the penial and urethral cavernous body when necessary[10].

For less-likely removable strangulating objects, direct cutting is recommended. Under these circumstances, the hardness and thickness of the material should be taken into consideration. For non-metallic incarcerations, such as hair tourniquet syndrome[2], rubber bands for disease prevention[2], plastic bottles for sexual entertainment[12], or seal rings[13], the treatments are reported to be comparatively more straightforward. However, as the strangulating objects had a certain degree of deformability, it is crucial to restore the deformed penis after removing the strangulating objects. Due to the metallic hoop’s hardness and thickness, treatments on metallic incarcerations are
more complicated. Previous literature mentioned various surgical tools, mostly from orthopedics and dentistry, such as motor-operated emery wheel machine, metal cutter, grinder, hacksaw, fretsaw, industrial-grade steel bolt cutters, and marble cutting tool [4,14,15]. In extreme cases such as strangulation by axletree[16] or hammerhead, cautious planning is needed before violent cutting. The heat originating from the persistent cutting procedure could cause burn injury even with additional irrigation. Subsequently, the operation might be performed in a de-gloving way[16], which can be decomposed into three steps: (1) De-gloving the skin distal to the strangulated area till the coronal part; (2) Moving the constrictive object towards the distal end; and (3) Suturing the edge of the skin back.

Extra operations are required in exceptional situations, such as PI with shallow ulcerations or urinary tract fistulae. Ulceration indicates the necrosis of penial skin or partial corpus cavernosum. Thereafter, the necrotic part needs to be debrided first. However, if the wound defect is too large to be sutured, a skin graft with radial forearm flap neophallus might be required. If deep necrosis is found in the urethra, partial or entire penectomy might be necessary[9,17,18].

There were three main benefits of using a fretsaw in this case. First, compared with a dental drill and other electric equipment, the initiation, cessation, and alteration of cutting direction could be adjusted more responsively when deploying a fretsaw. Second, there would be no inertia and electric sparks because hands drove the fretsaw. Last but not least, because the cutting direction was from the inner layer to the outer surface, the accidental injury caused by the damage of the metal structure would be avoided.

Nevertheless, the cutting efficiency of using a fretsaw is comparatively low, as it is purely powered by hands. Continuously cutting for several minutes is tiring, and thereafter loss of controllability might occur. Same as other methods, thermal damage could not be avoided. Hence, an assistant must continuously spray normal saline with a syringe to cool the metal surface.

Several limitations should be noted. First, due to the rarity of PI, more cases are awaiting to be summarized to increase credibility and generality. Specific consideration should be taken regarding patient status, the degree of edema, and the material of the incarcerating object. Systematic reviews are called for to establish higher-level evidence. Second, specific steps, in this case, could be optimized, such as a bacterial culture could be performed in case of severe postoperative skin infection, and the postoperative daily observation of the wound might be better recorded.

CONCLUSION

In conclusion, the selection of cutting tools depends on the strangulating object and the availability of equipment. Meanwhile, the concrete operation also relies on the severity of penial damage. The urination function may not be affected after three months of incarceration like in this case, but prudent measures and sufficient preparations should be taken preoperatively. Even though using a fretsaw in treating PI is comparatively less efficient, it is feasible and safe.
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