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ORIGINAL ARTICLE

Retrospective Cohort Study

Efficacy of cognitive-behavioral therapy combined with habit reversal training on anxiety disorders in children with Tourette's syndrome

Yan-Zhen Wang, Xi Zhang, Xin-Min Han

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Abstract

BACKGROUND

Cognitive-behavioral therapy (CBT) and habit reversal training (HRT) have shown application potential in addressing tic symptoms and comorbid psychiatric conditions. Despite their theoretical potential, empirical evidence on their combined efficacy remains limited.

AIM

To evaluate the efficacy of CBT combined with HRT on anxiety disorders in children with Tourette's syndrome (TS).

METHODS

Clinical data of children with TS admitted to our hospital from January 2022 to June 2023 were collected, and the patients were grouped into the conventional therapy (control) group and the CBT combined with HRT group. Baseline characteristics, anxiety scores, tic severity scores, treatment adherence, and parental satisfaction were assessed. Statistical analysis was performed using t-tests, chi-square tests, and correlation analysis.

RESULTS

A total of 136 patients, including 65 patients in the control group and 71 patients in the CBT combined with HRT group, were included. The CBT combined with HRT group showed remarkable improvements compared with the control group. Post-intervention assessment revealed a decrease in anxiety scores from 63.52 ± 1.81 to 40.53 ± 1.64 (t = 2.022, P = 0.045), and the Yale Global Tic Severity Scale total score decreased from 22.14 ± 5.67 to 16.28 ± 4.91 (t = 2.288, P = 0.024).

Treatment adherence was significantly higher in the CBT combined with HRT group (85.47 ± 7.62%) compared with the control group (82.32 ± 6.54%; t = 2.596, P = 0.010). Parental satisfaction scores were also higher in the CBT combined with HRT group (8.69 ± 1.77) compared with the control group (7.87 ± 1.92; t = 2.592, P = 0.011).

CONCLUSION

This study demonstrates that CBT combined with HRT significantly reduces anxiety symptoms and tic severity in children with TS, with higher treatment adherence and parental satisfaction. These findings support the potential application of this comprehensive therapeutic approach for TS treatment.

Key Words: Tourette's syndrome; Cognitive-behavioral therapy; Habit reversal training; Efficacy evaluation; Anxiety disorders

Core Tip: This study aimed to evaluate the relationship between the levator ani muscle hiatus (LH) area and pelvic organ prolapse (POP) in parturients with gestational diabetes mellitus using perineal ultrasound. Conclusion: Three-dimensional perineal ultrasonography evaluation of the LH size and shape changes can effectively diagnose POP.

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INTRODUCTION

Tourette's syndrome (TS) is a complex neurodevelopmental disorder characterized by multiple motor and one or more vocal tics, with onset in childhood or adolescence[1]. The manifestation of tics can be highly variable, in terms of their nature (motor *vs* vocal tics) and severity, affecting the quality of life and psychosocial functioning of those diagnosed[2]. Apart from the primary tic symptoms, TS is frequently associated with comorbid psychiatric conditions and notable anxiety disorders, which can exacerbate the overall disease burden on affected individuals[3]. Anxiety disorders in children with TS are particularly concerning as they can interfere with social development, educational attainment, and overall well-being[4].

The conventional therapeutic approach to managing TS focuses on pharmacological treatment to mitigate the severity of tics[5,6]. However, medications such as antipsychotics, which is often used in treatment, can have a variety of adverse effects that may dissuade patients and their families from pursuing these options[7]. Given these challenges, alternative treatment modalities to address tics and the often-associated psychiatric comorbidities have been receiving increasing interest[8].

Cognitive-behavioral therapy (CBT) has emerged as a promising psychological intervention for a range of psychiatric disorders, including anxiety[7,9]. It is grounded in the conceptual framework that maladaptive thoughts and beliefs underlie and perpetuate psychological symptoms[10]. CBT works by helping individuals identify and challenge these unhelpful thought patterns, thereby reducing psychiatric symptoms and enhancing coping strategies[11]. Habit reversal training (HRT), another behavioral intervention, specifically targets the tic symptoms of TS by increasing the awareness of tic behaviors and teaching competing responses[12,13]. By combining CBT and HRT, there exists a potentially synergistic therapeutic approach that targets the tic symptoms and psychiatric comorbidities of TS, particularly anxiety disorders[13].

The rationale for combining CBT with HRT in treating children with TS stems from the multidimensional nature of the disorder[14]. Tics in TS were not merely neurological symptoms but were significantly influenced by psychological stressors, with anxiety known to exacerbate tic severity[15]. By addressing the psychological aspects of the disorder through CBT, alongside the specific tic behaviors through HRT, a more holistic approach to treatment was offered[16]. Such an approach not only aims at reducing tic severity but also at improving the overall mental health and quality of life of the affected children[17].

Despite the theoretical potential of this combined treatment modality, empirical evidence on its efficacy remains relatively limited[13]. Given the chronic nature of TS and the impact of psychiatric comorbidities such as anxiety disorders on treatment outcomes, understanding these aspects of the therapeutic process is essential. Thus, this study aimed to fill these gaps by conducting a rigorous evaluation of the efficacy of CBT combined with HRT on anxiety disorders in children with TS. By leveraging a retrospective cohort design, this research seeks to compare the outcomes of a CBT and HRT combined treatment modality against conventional therapy, focusing on measures of anxiety, tic severity, treatment adherence, and parental satisfaction.

MATERIALS AND METHODS

Study design

This study was retrospective in nature. Clinical data of children with TS admitted to our hospital from January 2022 to June 2023 were collected, and the patients were grouped into the conventional therapy (control) group and the CBT combined with HRT group. The patient selection involved several steps to ensure respect for and consideration of patient preferences. First, the physicians provided comprehensive information about existing treatment options, including their benefits and potential risks, to all patients in a clear and understandable manner, ensuring that the patients fully comprehended their choices. Subsequently, mutual decision-making between the patients and physicians, considering the patients' medical conditions, personal values, and preferences, involved open and honest discussions of available treatment modalities. This study was approved by the Ethics Committee of Affiliated Hospital of Nanjing University of Chinese Medicine, and it obtained an informed consent form.

Eligibility and grouping criteria

The inclusion criteria were as follows: (1) Children diagnosed with TS in accordance with the diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[18]; (2) Normal intelligence; (3) Age between 4 and 14 years; (4) Normal physical function; (5) Symptoms of TS not attributable to the physiological effects of a substance (such as cocaine) or other conditions (such as Huntington's disease and viral encephalitis); (6) Moderate-to-severe TS, assessed using the Yale Global Tic Severity Scale (YGTSS) with a score greater than 20; (7) Completion of 6 months of follow-up; and (8) Complete medical records.

The exclusion criteria were as follows: (1) Tourette-like symptoms caused by conditions such as rheumatic chorea, Sydenham's chorea, Wilson's disease, encephalitis, or drug-induced disorders; (2) Concurrent severe primary diseases involving the cardiovascular, pulmonary, hepatic, renal, or hematopoietic systems; (3) Patients with additional diseases requiring specific treatment during the study, which could affect the primary diagnosis, or those with severe physical illnesses; and (4) Inability to adhere to the treatment plan.

Treatment approach

The control group received Clonidine transdermal patches (Shanxi Ruifulei Pharmaceutical Co., Ltd.), which were applied below the shoulder blade on the back and replaced every 7 days (alternating sides of the shoulder blade), concluding after 24 weeks. The Clonidine dosage was as follows: 1.0 mg per patch for body weight between 20 and 40 kg, 1.5 mg per patch for body weight between 40 and 60kg, and 2.0 mg per patch for body weight over 60 kg.

The CBT combined with HRT group underwent CBT combined with HRT, administered once a week for 60 minutes, concluding after 24 weeks. The cognitive-behavioral interventions were as follows: (1) Regular education for parents and children about TS, promoting understanding and support and dispelling misconceptions; (2) Encouraging children not to blame themselves for the disorder, to manage social interactions, and to build confidence in treatment; explaining the fluctuating nature of symptoms and the favorable overall prognosis to alleviate anxiety; (3) Encouraging appropriate physical activities while avoiding competitive or aggressive behaviors and stimuli such as violent media or gaming; and (4) Collaboratively identifying and addressing triggers for tic symptoms with family and therapists to develop coping strategies.

HRT: (1) Awareness training: Response description: Children were instructed to face a mirror and provide detailed descriptions of their tics, reenacting the tic movements; Response detection: When tics occur, the therapist promptly points them out to enhance the children's ability to notice their tics through this training; Early warning procedure: Children were taught to recognize the premonitory urges of tics, including the impulse to tic preceding the actual tic or the early signs of motor tics, and to identify the earliest premonitory signs when tics occur; Situational awareness training: The common situations triggering tics were determined through data analysis, which involves direct video feedback using video recorders and mirrors, as well as the use of smart wearable watches, small notebooks, and other devices to record tic occurrences; (2) Response competition training: Once children have developed a reliable ability to detect tics and premonitory urges, they were educated to perform response competition every time premonitory urges or tics occur, maintaining this competition for 1-3 minutes or until the urge to tic subsides. Response competition behavior should meet the following criteria: Be neurologically opposite; Be sustainable for several minutes; Produce equal muscle tension as the target movement; Not attract attention in social activities, easily compatible with ongoing normal activities, but incompatible with habits (referring to tics); For muscular tics, the behavior must strengthen muscle movements that compete with the tic; (3) Anxiety management techniques: Deep breathing, progressive muscle relaxation, and visualization were the commonly used anxiety management techniques for tic disorders. For children experiencing anxiety or stress, integrating relaxation techniques were an essential part of HRT; and (4) Motivational and assistance techniques: Reviewing the troubles of habits: In the early stages of treatment, children and therapists create a "Tic Trouble Chart," listing all the negative impacts of tics (such as embarrassment, discomfort, interference, and need for medical attention). Occasionally, reviewing the chart continues until improvements were made to render the chart obsolete. Apart from breaking the children's denial of symptoms and reinforcing treatment motivation, the chart can also serve as a step for them to explore the causal relationship of tic disorders and promote a more realistic acceptance of their situation; Tic severity rating: At the beginning of treatment, children and therapists create a comprehensive list of the child's tics, and then they rate each tic on a scale of 1 to 10 based on the extent of disturbance or distress caused by the tic (10 points = most distressing). For young children or those who deny that tics cause distress, classifying tic severity based on the frequency of occurrence rather than distress and using different measurement criteria were necessary. Then, the tic symptoms were arranged in the order of least to most distressing (or frequency). Reviewing this chart and reassessing the

tic levels before each treatment provide a systematic and immediate method for setting treatment goals and challenges; Social support: If a child successfully applies awareness skills or completes other treatment tasks, then the child has a period free of tics and adheres to the treatment protocol. Other family members, sometimes even teachers and friends, should commend and support the child; Behavioral reward system: A systematic reward system was developed to incentivize and enhance the compliance of children who complete the behavioral treatment plan.

Data collection

Through systematic case retrieval, the general information of the pediatric patients was gathered, including age, gender, body mass index (BMI), age of onset, duration of TS and coprolalia, comorbidities such as ADHD and OCD, previous treatment rates, parental education level, parental marital status, family history of ADHD, family history of OCD, and family history of TS and coprolalia.

The anxiety status of the two groups of patients was assessed before treatment and at the 24th week of treatment using the Self-rating Anxiety Scale (SAS). The SAS consists of 20 items with a total score of 100, covering emotional symptoms, physical dysfunction, mental agitation, and psychological distress. The anxiety level was inversely related to the total score; scores below 50 indicate no anxiety, 50-59 indicate mild anxiety, 60-69 indicate moderate anxiety, and 70 and above indicate severe anxiety. The scale demonstrated a Cronbach's alpha coefficient of 0.849[19].

Compared with the YGTSS scores, the YGTSS score was obtained by combining the scores for motor tics, vocal tics, and functional impairment. Higher YGTSS scores indicate more severe symptoms, with a maximum score of 100 and a Cronbach's alpha coefficient of 0.84[20].

Clinical symptoms of the enrolled subjects were collected using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) assessment. The Y-BOCS includes 10 items, each rated on a five-point scale (0-4) to evaluate the severity of obsessions and compulsions, with a total score of 40. Higher scores represent more severe symptoms, with a Cronbach's alpha coefficient of 0.875[21].

Patients were evaluated using the Clinical Global Impression-Severity (CGI-S) scale, which measures illness severity on a scale of 0-7, with scores inversely correlated to treatment effectiveness and a Cronbach's alpha coefficient of 0.839[22].

The Family Adaptability and Cohesion Evaluation Scale (FACES-III) was used to assess emotional connectedness and adaptability among family members, comprising 20 items with a five-point scoring system (1 being "never" and 5 being "always"). Higher scores indicate greater family cohesion and adaptability.

At week 24 post-treatment, patient adherence was evaluated using the Treatment Adherence Rating Scale, which consists of five items assessing compliance with regard to agreement and adherence to psychological therapy on a scale of 0% to 100%. A higher total score indicates better adherence to psychological therapy. In addition, patient treatment satisfaction was assessed through a self-made questionnaire, which results in a 10-point score. The scores were categorized as follows: highly satisfied (8-10 points), satisfied (7-8 points), fair (6-7 points), and dissatisfied (< 6 points). The statistical assessment of patient treatment recommendations was also included.

Data cleaning and management

Before conducting data analysis, this study performed a standardized data cleaning process to identify and correct any inconsistencies, errors, or missing values. This process involved thorough examination of the dataset, removal of duplicate entries, correction of data input errors, and handling missing values. In Python 3.6.0, the Impyute library was utilized for KNN imputation to fill in missing values. Initially, a basic mean imputation was created in the complete list to construct a KDTree. Subsequently, the KDTree was used to calculate the nearest distances (NN) and find the K nearest points, followed by taking the weighted average of these points. The missing data were kept within 5% to control potential selection bias and underwent sensitivity analysis. The outcomes of loss to follow-up cases were calculated separately on the basis of the worst and best outcomes. If no significant difference was observed, then the loss to follow-up had minimal impact on the conclusions, thereby ensuring the reliability of the conclusions. The final output consisted of the results after filling in the missing values.

Post-hoc analysis

Using G*Power 3.1.9.7, the "Means: Difference between two independent means (two groups)" option based on t-tests was used for post hoc analysis, with two-tailed mode, effect size $d = 0.6$, α err prob = 0.05. Subsequently, the sample sizes of the two groups were input to calculate power (1-β err prob), resulting in a power value of 0.934.

Statistical analysis

The data were analyzed using SPSS 29.0 statistical software (SPSS Inc., Chicago, IL, United States). Categorical data were represented as [n (%)]. The χ^2 test was applied with the basic formula when the sample size was ≥ 40 and the theoretical frequency T was ≥ 5, with the test statistic represented by χ^2. When the sample size was ≥ 40 but the theoretical frequency was $1 \leq T < 5$, the χ^2 test was adjusted using the correction formula. Statistical analysis for cases where the sample size was < 40 or the theoretical frequency was $T < 1$ was conducted using the Fisher's exact probability method. Continuous variables underwent normal distribution testing using the Shapiro-Wilk method. For normally distributed continuous data, the format (mean ± SD) was used. Non-normally distributed data were analyzed using the Wilcoxon rank-sum test, and the [median (25% quantile, 75% quantile)] was used for presentation. Statistical significance was set at $P < 0.05$. Correlation analysis used Pearson correlation analysis for continuous variables and Spearman correlation analysis for categorical variables.

RESULTS

Demographic and basic data

A total of 136 patients, including 65 patients in the control group and 71 patients in the CBT combined with HRT group, were included. The baseline characteristics of the participants in the study are presented in Table 1. These two groups had similar baseline characteristics, including age, gender distribution, BMI, age of onset of TS, duration of TS, comorbid ADHD, comorbid OCD, previous treatment, parental education, parental marital status, family history of ADHD, family history of OCD, and family history of TS. No statistically significant differences in any of the baseline characteristics were observed between the two groups, as evidenced by the non-significant *P*-values for all comparisons ($P > 0.05$).

Pre-intervention anxiety and tic severity scores

The pre-intervention anxiety and tic severity scores for the control group and the CBT combined with HRT group are summarized in Table 2. No statistically significant differences in the anxiety score, YGTSS total score, Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score, CGI-S score, and FACES IV score were found between the two groups, as indicated by non-significant *P*-values for all comparisons ($P > 0.05$). The mean scores for anxiety and tic severity were comparable between the control and intervention groups before the intervention.

Post-intervention anxiety and tic severity scores

Statistically significant improvements in anxiety and tic severity scores were observed following the intervention with CBT combined with HRT compared with the control group (Table 3). In particular, post-intervention assessment revealed a decrease in anxiety scores from 40.53 ± 1.64 to 39.97 ± 1.58 in the CBT combined with HRT group, with a t-value of 2.022 and a *P*-value of 0.045. Furthermore, the YGTSS total score decreased from 16.28 ± 4.91 to 14.49 ± 4.12 ($t = 2.288$, $P = 0.024$); the CY-BOCS total score decreased from 13.36 ± 3.82 to 11.75 ± 3.49 ($t = 2.555$, $P = 0.012$); the CGI-S score decreased from 2.31 ± 0.68 to 2.08 ± 0.59 ($t = 2.146$, $P = 0.034$), and the FACES IV score increased from 24.77 ± 6.28 to 27.48 ± 5.93 ($t = 2.586$, $P = 0.011$). These findings indicate that CBT combined with HRT has a beneficial impact on anxiety and tic severity in children with TS.

Treatment adherence

Upon evaluating treatment adherence, the group undergoing CBT combined with HRT demonstrated significantly higher adherence compared with the control group (Figure 1). In particular, the CBT combined with HRT group exhibited a treatment adherence of 85.47% ± 7.62%, whereas the control group showed a treatment adherence of 82.32% ± 6.54% ($t = 2.596$, $P = 0.010$).

Parental satisfaction survey results

Analysis of the parental satisfaction survey results indicated notable findings regarding the perception of the CBT combined with HRT intervention (Table 4). The CBT combined with HRT group demonstrated higher levels of satisfaction, with a satisfaction score of 8.69 ± 1.77 compared with 7.87 ± 1.92 in the control group, resulting in a t-value of 2.592 and a *P* value of 0.011. Furthermore, a larger percentage of parents in the CBT combined with HRT group expressed willingness to recommend the intervention, with 66 parents (92.96%) in favor, compared with 51 parents (78.46%) in the control group, resulting in a χ^2 value of 4.788 and a *P* value of 0.029. These results indicate a favorable parental perception of the CBT combined with HRT intervention, indicating higher satisfaction and a greater likelihood of recommending the intervention to others.

Correlation analysis between CBT combined with HRT treatment and post-intervention anxiety and tic severity scores

Correlation analysis revealed associations between CBT combined with HRT treatment and post-intervention anxiety and tic severity scores (Table 5). The analysis demonstrated statistically significant negative correlations among the CBT combined with HRT treatment and anxiety scores ($r = -0.172$, $R^2 = 0.03$, $P = 0.045$), YGTSS total score ($r = -0.195$, $R^2 = 0.038$, $P = 0.023$), CY-BOCS total score ($r = -0.216$, $R^2 = 0.047$, $P = 0.011$), and CGI-S score ($r = -0.183$, $R^2 = 0.034$, $P = 0.033$). Moreover, a statistically significant positive correlation was observed between the CBT combined with HRT treatment and FACES IV score ($r = 0.219$, $R^2 = 0.048$, $P = 0.011$), indicating the potential impact of the intervention on anxiety and tic severity measures.

DISCUSSION

This study aimed to evaluate the efficacy of CBT combined with HRT on anxiety disorders in children diagnosed with TS. The results indicate significant improvements in anxiety scores and tic severity measures in the group that underwent CBT combined with HRT, compared with the control group receiving conventional therapy.

The choice of combining CBT with HRT stems from their respective efficacy in managing tic disorders and associated psychological conditions, such as anxiety[23]. CBT was known for its success in modifying thought patterns and behaviors that contribute to psychological stress[24]. On the contrary, HRT focuses on increasing awareness of tic behaviors and implementing competing responses. The integration of these two therapies targets the dual aspects of TS-its physical manifestations and associated psychological impacts, thereby providing a comprehensive treatment approach [25].

Table 1 Baseline characteristics of participants

Characteristic	Control (*n* = 65)	CBT combined with HRT (*n* = 71)	t/χ^2	*P* value
Age (years)	11.54 ± 2.31	11.72 ± 2.13	0.465	0.643
Gender [male/female, *n* (%)]	40 (61.54)/25 (38.46)	45 (63.38)/26 (36.62)	0.002	0.965
BMI	16.73 ± 2.14	17.24 ± 2.35	1.326	0.187
Age of onset (years)	8.74 ± 2.46	8.61 ± 2.38	0.302	0.763
Duration of Tourette's syndrome (months)	16.28 ± 4.67	15.92 ± 5.01	0.434	0.665
Comorbid ADHD, *n* (%)	17 (26.15)	20 (28.17)	0.005	0.943
Comorbid OCD, *n* (%)	11 (16.92)	10 (14.08)	0.048	0.826
Previous treatment, *n* (%)	27 (41.54)	27 (38.03)	0.059	0.808
Parental education			None	0.779
High school or less	23 (35.38)	20 (28.17)		
Some college	16 (24.62)	21 (29.58)		
Bachelor's degree	13 (20.00)	18 (25.35)		
Master's degree	10 (15.38)	8 (11.27)		
Doctoral degree	3 (4.62)	4 (5.63)		
Parental marital status, *n* (%)			None	0.919
Married	45 (69.23)	52 (73.24)		
Divorced/separated	10 (15.38)	9 (12.68)		
Single parent	7 (10.77)	6 (8.45)		
Other	3 (4.62)	4 (5.63)		
Family history of ADHD, *n* (%)	7 (10.77)	9 (12.68)	0.006	0.938
Family history of OCD, *n* (%)	7 (10.77)	9 (12.68)	0.006	0.938
Family history of Tourette's syndrome, *n* (%)	16 (24.62)	21 (29.58)	0.209	0.648

BMI: Body mass index; CBT: Cognitive-behavioral therapy; HRT: Habit reversal training.

Table 2 Pre-intervention anxiety and tic severity scores

Measure	Control (*n* = 65)	CBT combined with HRT (*n* = 71)	*t* value	*P* value
Anxiety score	63.52 ± 1.81	64.03 ± 1.67	1.703	0.091
YGTSS total score	22.14 ± 5.67	21.89 ± 5.12	0.274	0.785
CY-BOCS total Score	18.25 ± 4.92	18.51 ± 4.57	0.324	0.747
CGI-S score	3.48 ± 0.82	3.56 ± 0.75	0.632	0.528
FACES IV score	15.89 ± 5.12	14.72 ± 4.78	1.374	0.172

CBT: Cognitive-behavioral therapy; HRT: Habit reversal training; YGTSS: Yale Global Tic Severity Scale; CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale; CGI-S: Clinical Global Impression-Severity.

Consistent with existing literature[24], this study found that the combination of CBT and HRT effectively reduced anxiety levels in pediatric patients with TS. Studies have previously shown that CBT can reduce symptoms of anxiety and improve the overall quality of life in this patient population[25,26]. For example, Billnitzer and Jankovic[27] highlighted the positive impact of behavioral interventions on tic severity, advocating for their early implementation in the therapeutic process.

Understanding the enduring effects and sustainability of the intervention over an extended period is important to ascertain its continued efficacy. In addition, investigating potential moderators of treatment response, such as age, gender, or specific tic symptomatology, could provide valuable insights into the nuanced factors influencing the effectiveness of the combined therapeutic approach. Furthermore, comparative effectiveness studies comparing CBT combined

Table 3 Post-intervention anxiety and tic severity scores

Measure	Control (*n* = 65)	CBT combined with HRT (*n* = 71)	*t* value	*P* value
Anxiety score	40.53 ± 1.64	39.97 ± 1.58	2.022	0.045
YGTSS total score	16.28 ± 4.91	14.49 ± 4.12	2.288	0.024
CY-BOCS total Score	13.36 ± 3.82	11.75 ± 3.49	2.555	0.012
CGI-S score	2.31 ± 0.68	2.08 ± 0.59	2.146	0.034
FACES IV score	24.77 ± 6.28	27.48 ± 5.93	2.586	0.011

CBT: Cognitive-behavioral therapy; HRT: Habit reversal training; YGTSS: Yale Global Tic Severity Scale; CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale; CGI-S: Clinical Global Impression-Severity.

Table 4 Parental satisfaction survey results

Measure	Control (*n* = 65)	CBT combined with HRT (*n* = 71)	t/χ^2	*P* value
Satisfaction score (1-10)	7.87 ± 1.92	8.69 ± 1.77	2.592	0.011
Would recommend, *n* (%)	51 (78.46)	66 (92.96)	4.788	0.029

CBT: Cognitive-behavioral therapy; HRT: Habit reversal training.

Table 5 Correlation analysis between cognitive-behavioral therapy combined with habit reversal training treatment and post-intervention anxiety and tic severity scores

Measure	r	R^2	*P* value
Anxiety score (1-10)	−0.172	0.03	0.045
YGTSS total score	−0.195	0.038	0.023
CY-BOCS total Score	−0.216	0.047	0.011
CGI-S score	−0.183	0.034	0.033
FACES IV score	0.219	0.048	0.011

YGTSS: Yale Global Tic Severity Scale; CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale; CGI-S: Clinical Global Impression-Severity.

with HRT with other therapeutic modalities could provide comprehensive insights into the relative benefits and limitations of different treatment approaches, aiding in the development of evidence-based guidelines for the management of TS and anxiety disorders in children. These future research directions could contribute to a more nuanced and tailored approach to treatment while enhancing the overall understanding of the optimal management of TS and its comorbidities.

Moreover, the finding that CBT combined with HRT results in better treatment adherence and parental satisfaction further strengthens the case for this treatment modality. Previous research[28] has emphasized the importance of patient and caregiver engagement in the treatment process, as it directly influences treatment outcomes. The high adherence rates observed in this study could be attributed to the active involvement and empowerment of children and their families throughout the treatment process, enhancing their commitment and satisfaction.

From a theoretical standpoint, this study contributes to the understanding of how comprehensive behavioral therapies can modulate the manifestation of TS and its comorbidities, such as anxiety disorders. The positive correlation between CBT combined with HRT and reduced anxiety and tic severity corroborates the notion that these therapeutic approaches can alter the neurological and psychological underpinnings of this condition.

The remarkable reduction in anxiety symptoms and tic severity in children with TS following a CBT combined with HRT intervention can be understood through several interconnected mechanisms. These reasons were rooted in the psychological framework of TS and the neurobiological underpinnings that govern its manifestation.

In the HRT framework, HRT focuses on increasing patient's awareness of their tic behaviors and urges and then teaches competing responses. By consciously implementing a behavior that is physically incompatible with the tic, the patient can inhibit the manifestation of tic. This process reduces tic severity while empowering the child, leading to reduced anxiety over the loss of control associated with tic outbreaks. In addition, many children with TS experience premonitory urges, such as uncomfortable sensations that precede tics[29]. HRT helps children recognize these urges and

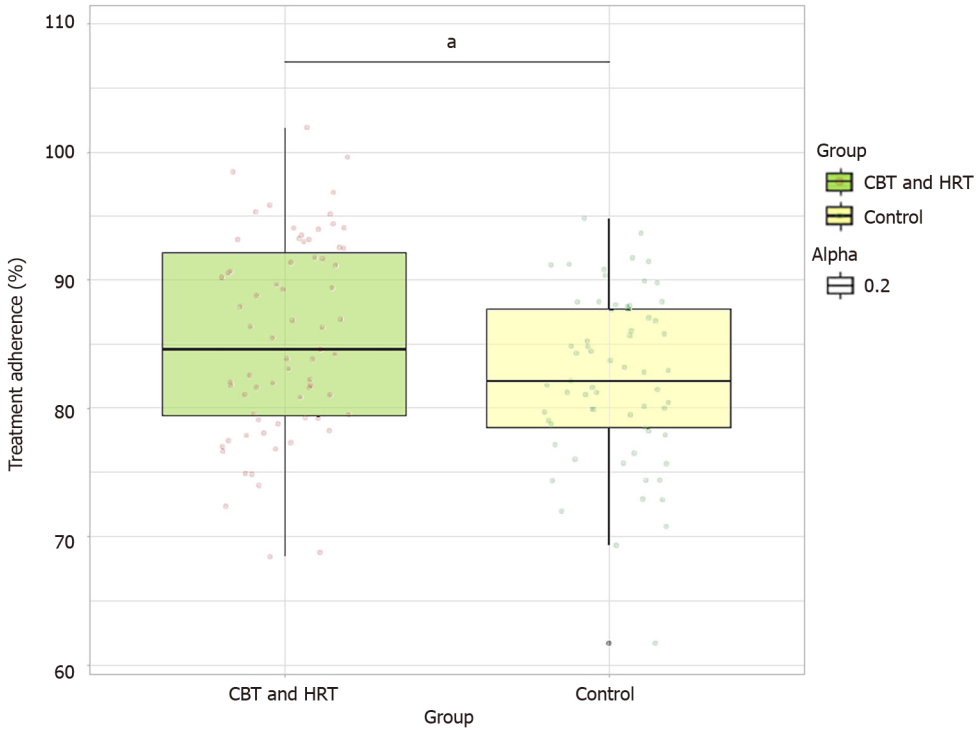

Figure 1 Comparison of treatment adherence between cognitive-behavioral therapy combined with habit reversal training and conventional therapy groups in children with Tourette's syndrome. CBT: Cognitive-behavioral therapy; HRT: Habit reversal training. [a]*P* < 0.05.

apply techniques to alleviate them before they escalate into full-blown tics. Reducing these premonitory urges can decrease the severity of tics and the anxiety associated with anticipating these urges.

In neurobiological mechanisms, emerging research suggests that behavioral therapies, including CBT and HRT, can modulate the neural circuits implicated in TS[30]. These therapies may help normalize the functioning of cortico-striato-thalamo-cortical circuits, which were often dysregulated in TS[31]. Improved regulation of these neural pathways can lead to reduced tic severity and can decrease anxiety by enhancing the overall neurological function and emotional regulation[32,33]. In addition, stress is known to exacerbate tics and anxiety[34]. CBT and HRT can effectively reduce stress levels, potentially through the downregulation of the hypothalamic-pituitary-adrenal axis and the modulation of neurotransmitter systems involved in stress and anxiety, such as serotonin and dopamine[34]. By reducing stress, these therapies indirectly contribute to a decrease in tic severity and anxiety symptoms.

Practically, the implications of these findings were far-reaching. Implementing CBT combined with HRT as a standard treatment option could transform the therapeutic landscape for children with TS. By prioritizing treatments that show higher efficacy and satisfaction among patients and caregivers, healthcare providers can improve treatment outcomes and the quality of life for this population.

However, this study has some limitations. The retrospective nature of the study and the reliance on existing medical records might introduce biases related to data accuracy and completeness. In addition, although the study's sample size is adequate for statistical analysis, it might not fully capture the diversity and complexity of TS presentations in the broader population.

Further research, particularly prospective studies with larger and more diverse cohorts, is necessary to validate these findings. Investigating the long-term outcomes of CBT combined with HRT, beyond the 24-week follow-up period, would provide insights into the enduring effects of this treatment modality. In addition, exploring individual components' contributions to the overall efficacy of the combined treatment could refine and optimize therapeutic protocols.

CONCLUSION

This study demonstrates that CBT combined with HRT remarkably reduces anxiety symptoms and tic severity in children with TS. The observed improvements in treatment adherence and parental satisfaction further support the application of this comprehensive therapeutic approach. These findings indicate that healthcare providers who manage children with TS and comorbid anxiety should consider integrating CBT combined with HRT as a first-line or adjunctive treatment modality. Given the potential impact of this combined approach on reducing anxiety and tic severity, healthcare providers should be encouraged to undergo specific training to effectively implement and integrate CBT and HRT into their practice. Furthermore, promoting active involvement of parents and caregivers in the treatment process is crucial for healthcare providers, emphasizing the importance of their support and adherence.

FOOTNOTES

Author contributions: Wang YZ and Han XM designed the experiment and conducted clinical data collection; Zhang X and Han XM performed postoperative follow-up and recorded data; Wang YZ and Han XM conducted a number of collation and statistical analysis; all authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Impact of comorbid subthreshold depressive symptoms on cancer-related fatigue and complications in adults with leukemia

Yue-Xian Liu, Juan Wang

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Abstract

BACKGROUND

Patients not only experience symptoms caused by cancer but also suffer from the accompanying psychological pain. Therefore, these patients do not have high quality of life. According to the World Health Organization, the incidence of leukemia in China in 2020 was 5.1/100000, the mortality rate was 3.3/100000, and the prevalence rate was 16.7/100000. Therefore, it is important to examine the influence of comorbid subthreshold depressive symptoms on leukemia patients.

AIM

To determine the impact of comorbid subthreshold depressive symptoms on cancer-related fatigue and complications in leukemia patients, thereby providing a basis for early diagnosis and treatment in clinical practice.

METHODS

A questionnaire survey was conducted among leukemia patients admitted to a tertiary hospital in Xi'an, Shaanxi Province, China, from August 2022 to December 2023. Patients with a score > 16 on the Chinese Classification of Mental Disorders (CCMD-3) and a Hamilton Depression Rating Scale score of 8-17 were classified as the subthreshold depressive group (n = 95), while 100 leukemia patients admitted during the same period were classified as the control group. Data were collected using Epidata 3.1 software, and comparisons were made between the two groups regarding general clinical data, the Piper Fatigue Scale (PFS), the Pittsburgh Sleep Quality Index (PSQI), the Numeric Rating Scale for pain assessment, laboratory indicators, and the occurrence of complications.

RESULTS

In this survey, 120 leukemia patients with depression were preliminarily screened, 95 patients with subthreshold depression were ultimately selected as the subthreshold depression group, and 100 leukemia patients admitted during the same period were enrolled as the normal group. Comparison of basic clinical data

between the two groups revealed no significant differences in age, sex, body mass index, cognitive function, or comorbidity with other chronic diseases. However, there were statistically significant differences in the use of radiotherapy and regular exercise between the two groups ($P < 0.05$). Comparisons of scales and laboratory indicators revealed no significant differences in albumin or PSQI scores between the two groups, but there were statistically significant differences in pain scores, PSQI scores, PFS scores, hemoglobin levels, and C-reactive protein levels ($P < 0.05$). Spearman's correlation analysis indicated that cancer-related fatigue was correlated with age, hemoglobin levels, C-reactive protein levels, pain, and regular exercise among leukemia patients with subthreshold depression. Multivariate regression analysis revealed that advanced age, combined radiotherapy, pain, and low hemoglobin levels were risk factors for cancer-related fatigue in leukemia patients with comorbid subthreshold depression, while regular exercise was a protective factor against cancer-related fatigue. Follow-up comparisons revealed a significantly lower overall incidence of complications in the control group (4%) than in the depressive group (24.21%; $P < 0.001$).

CONCLUSION

Leukemia patients with comorbid subthreshold depressive symptoms experience more severe cancer-related fatigue and a higher incidence of complications. These findings may be related to advanced age, combined radiotherapy, pain, and low hemoglobin levels, while regular exercise may effectively alleviate symptoms.

Key Words: Subthreshold depression; Leukemia; Cancer-related fatigue; Complications; Minor depression

Core Tip: In this randomized controlled trial, leukemia patients with subthreshold depression were compared with leukemia patients without subthreshold depression. Multiple regression analysis revealed that advanced age, combined radiotherapy, pain, and low hemoglobin were risk factors for cancer-related fatigue in leukemia patients with subthreshold depression, and regular exercise was a protective factor against cancer-related fatigue. The total incidence of leukemia complications in the control group (4%) was significantly lower than that in the depressive group (24.21%).

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INTRODUCTION

Subthreshold depression, also known as minor depression, refers to a suboptimal health state or a subgroup of individuals who exhibit depressive mood manifestations but do not meet the diagnostic criteria for major depressive disorder in terms of clinical symptoms, quantity, or nature[1]. Epidemiological surveys have shown that subthreshold depression is prevalent in the general population, with a prevalence ranging from 5% to 24%[2], which is significantly greater than that of major depressive disorder. The symptoms of subthreshold depression are subtle and often go unnoticed, with patients often becoming aware of them due to incidental factors and attributing them to specific stages or adverse events. Underdiagnosis or misdiagnosis is common in this condition. If left uncorrected and untreated, subthreshold depression symptoms can worsen, leading to major depressive disorder. Compared to the general population, individuals with subthreshold depression have a greater likelihood of developing major depression within one year, and this relationship is even stronger among cancer patients[3]. In recent years, both domestic and international scholars have conducted extensive research on subthreshold depression in cancer patients with the aim of increasing knowledge regarding this condition and finding appropriate ways to correct patients' adverse psychological states, thereby improving their quality of life[4]. The current study aimed to explore the impact of comorbid subthreshold depression on cancer-related fatigue and complications among leukemia patients. The findings are reported as follows.

MATERIALS AND METHODS

General information

This study employed a randomized controlled design to examine leukemia patients who sought treatment for depressive symptoms at Central Hospital Affiliated with Shandong First Medical University from August 2022 to December 2023.

The sample size for this study was estimated based on the requirements of the prevalence rate: $n =$, $\alpha = 0.05$, two-sided $Z_{a/2} = 1.96$. P represents the overall occurrence rate of the investigated phenomenon in the target population, which, in

this study, is the occurrence rate of cancer-related fatigue in leukemia patients. Through preliminary investigations, P was determined to be 78%, and δ represents the allowable error, which can be taken as 0.1 P, 0.15 P, or 0.2 P. In this study, δ was set as 0.1 P. The calculated sample size was 100 patients.

Inclusion and exclusion criteria

The inclusion criteria for patients were as follows: (1) Had a clear cytological or pathological diagnosis of leukemia[5]; (2) Met the diagnostic criteria for subthreshold depression, with a Chinese Classification of Mental Disorders (CCMD-3) score > 16 and a Hamilton Depression Rating Scale (HAMD) score between 8 and 17[6]; (3) Males or females aged between 18 and 80 years; (4) Had an estimated life expectancy of at least 6 months; (5) Had no cognitive impairment or ability to comprehend the nature of the study; and (6) Were willing to participate in the study, underwent relevant follow-ups, and signed an informed consent form.

The exclusion criteria were as follows: (1) Age less than 18 years; pregnant or lactating individuals; (2) Had comorbid severe mania, depression, anxiety disorders, or schizophrenia; and (3) Were deemed unsuitable for participation by the researchers.

Study design

Data from preadmission interviews or admission records of leukemia patients were collected and organized using Epidata 3.1 software. The data were double-recorded and cross-checked and then provided to the research team for further analysis.

Clinical information was recorded for evaluation, investigating the current status and influencing factors of cancer-related fatigue in leukemia patients. The evaluation included four aspects: (1) Sociodemographic characteristics, including age, sex, body mass index (BMI), marital status (married or in a relationship, single, widowed, separated, or divorced), and employment status (unemployed, employed); (2) Recording of comorbid chronic diseases prior to admission; and (3) Observational scales, including the 22-item Piper Fatigue Scale (PFS), the 18-item Pittsburgh Sleep Quality Index, and the Numeric Rating Scale (NRS). The PFS includes four dimensions (emotional, cognitive, behavioral, and sensory). Each item is rated on a scale of 0-10, representing the degree of impairment. A higher cumulative score indicates more severe fatigue (0, no fatigue; 1-3, mild fatigue; 4-6, medium fatigue; 7-10, severe fatigue). The items on the PSQI are grouped into seven different dimensions, with scores ranging from 0 to 3 and a total score of 21. A lower total score indicates better sleep quality. The NRS is used to assess the intensity pain on a scale from 0 to 10 (0 represented no pain, 1-3 indicated mild pain without sleep disturbance, 4-6 represented moderate pain with mild sleep disturbance, 7-9 indicated severe pain causing difficulty falling asleep or awakening during sleep, and 10 represented excruciating pain). Additionally, laboratory data, including complete blood count, C-reactive protein, *etc.*, were collected.

Statistical analysis

Statistical analysis was performed using SPSS 27.0 software, and image processing was conducted using GraphPad 8.0 software. For continuous variables, *t* tests were used for comparisons. For categorical variables, χ^2 or Fisher's exact tests were employed for comparisons. Spearman's correlation analysis was performed. Multiple linear regression analysis was also performed to identify risk factors for cancer-related fatigue. A statistical significance level of $P < 0.05$ was considered significant.

RESULTS

Basic clinical characteristics

A total of 120 leukemia patients with depressive symptoms were preliminarily screened in this study, with 10 patients scoring < 16 on the CCMD-3 scale, 8 patients scoring < 8 on the HAMD scale, and 5 patients excluded due to major depressive disorder. Ultimately, 97 individuals with subthreshold depression were selected. A questionnaire survey was conducted among these subthreshold depression patients, with 95 responses collected, resulting in a response rate of 99%. There were 95 valid questionnaires, yielding an effective response rate of 99%. One hundred leukemia patients without depression who were admitted during the same period composed the control group. A comparison of the basic clinical characteristics between the two groups revealed no significant differences in age, sex, BMI, cognitive function, or comorbid chronic diseases. However, there were statistically significant differences between the two groups in terms of combined radiotherapy and regular exercise ($P < 0.05$), as shown in Table 1.

Comparison of observational indicators

Comparisons of the scales and laboratory indicators between the two groups revealed no significant differences in albumin levels or PSQI scores. However, there were statistically significant differences between the two groups in terms of pain scores, PFS scores, hemoglobin levels, and C-reactive protein levels ($P < 0.05$), as shown in Table 2 and Figure 1.

Correlation analysis of PFS scores in leukemia patients with subthreshold depression

Spearman's correlation analysis was conducted to examine the correlation between subthreshold depression in leukemia patients and PFS score, as well as the correlations between cancer-related fatigue and age, hemoglobin levels, C-reactive protein levels, pain, and regular exercise. The results revealed a positive correlation between age and the total PFS score ($r = 0.741$, $P = 0.013$), a positive correlation between regular exercise and the total PFS score ($r = 0.602$, $P = 0.029$), a negative

Table 1 Comparison of basic clinical characteristics

	Subthreshold depression (*n* = 95)	Control (*n* = 100)	Statistic	*P* value
Age (years, mean ± SD)	65.3 ± 10.22	63.6 ± 12.4	0.585	0.561
Gender			χ^2 = 1.60	0.45
Male, *n* (%)	56 (58.94)	52 (52.00)		
Female, *n* (%)	39 (41.05)	48 (48.00)		
Marriage, *n* (%)			Fisher's exact test	0.307
Married	63 (66.32)	50 (50.00)		
Single	10 (10.52)	8 (8.00)		
Bereft	10 (10.52)	12 (12.00)		
Devoice	12 (12.65)	25 (25.00)		
Work status, *n* (%)			χ^2 = 0.804	0.423
Unemployed	79 (0.84)	80 (80.00)		
Employed	16 (0.17)	20 (20.00)		
Comorbid chronic disease, *n* (%)			χ^2 = 0.795	0.428
Yes	12 (12.65)	10 (10.00)		
No	83 (87.36)	90 (90.00)		
BMI (kg/m^2, mean ± SD)	24.23 ± 9.29	23.91 ± 10.22	0.868	0.386
Combined radiotherapy, *n* (%)			χ^2 = 2.227	0.028
Yes	33 (35.76)	7 (7.00)		
No	62 (65.26)	93 (93.00)		
Regular exercise, *n* (%)			χ^2 = 2.609	0.010
Yes	12 (12.82)	54 (54.00)		
No	83 (87.87)	46 (46.00)		

Table 2 Comparison of observational indicators between the two groups

	Subthreshold depression (*n* = 95)	Control (*n* = 100)	Statistic	*P* value
Pain score (score, mean ± SD)	3.98 ± 2.43	1.34 ± 0.2	35.918	0.000
PSQI (score, mean ± SD)	11.0 ± 3.1	9.8 ± 1.8	1.841	0.070
Piper Fatigue Scale score (score, mean ± SD)	7.2 ± 1.6	4.5 ± 1.4	4.410	0.000
Hemoglobin (g/L, mean ± SD)	60.24 ± 12.45	71.19 ± 15.34	1.011	0.000
Albumin (g/L, mean ± SD)	33.98 ± 15.66	34.45 ± 19.46	1.534	0.128
CRP (mg/L, mean ± SD)	8.13 ± 1.55	4.24 ± 1.42	2.832	0.005

PSQI: Pittsburgh Sleep Quality Index; CRP: C-reactive protein.

correlation between hemoglobin levels and the total PFS score (r = -0.667, P = 0.034), a positive correlation between C-reactive protein levels and PFS score (r = 0.463, P = 0.004), and no correlation between pain and the total PFS score (P > 0.05). The correlations between each factor and the total PFS score and the scores of each dimension are shown in Table 3.

Multivariate regression analysis of PFS scores in leukemia patients with subthreshold depression

Multivariate linear regression analysis was conducted with subthreshold depression as the dependent variable and age, concurrent radiotherapy, regular exercise, pain score, PFS score, hemoglobin level, albumin level, and C-reactive protein level as the independent variables. Variables including age, concurrent radiotherapy, regular exercise, depression score, and hemoglobin level were entered into the equation (P < 0.05). The multivariate linear regression equation was as follows: subthreshold depression (Y) = -497.82+ 6.662 × age + 153.09 × concurrent radiotherapy - 236.85 × regular exercise + 2.017 × depression score + 2.826 × hemoglobin level. The regression equation revealed that advanced age, concurrent

Table 3 Correlation analysis of Piper Fatigue Scale scores in leukemia patients

	PFS score	Emotion	Recognition	Behavior	Sensation
Age	0.741[a]	0.791[a]	0.753[a]	0.745[a]	0.736[a]
Pain	0.321	0.561	0.176	0.264	0.146
Hemoglobin	-0.667[a]	-0.447	-0.453	-0.681[a]	-0.636[a]
CRP	0.463[a]	0.328[a]	0.285	0.339	0.642[a]
Regular exercise	0.602[a]	0.561[a]	0.453	0.456	0.636[a]

[a]$P < 0.05$.

PFS: Piper Fatigue Scale; CRP: C-reactive protein.

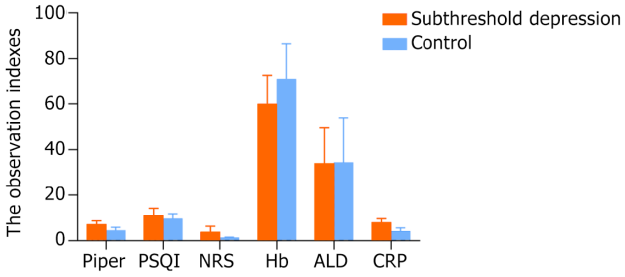

Figure 1 Comparison of observational indicators between the two groups. PSQI: Pittsburgh Sleep Quality Index; NRS: Numeric Rating Scale; Hb: Hemoglobin; ALD: Aldolase; CRP: C-reactive protein.

radiotherapy, pain, and low hemoglobin levels were risk factors for cancer-related fatigue, while regular exercise served as a protective factor against cancer-related fatigue (Table 4).

Comparison of leukemia complications between the two groups

After conducting follow-up comparisons in this study, it was found that the overall incidence of leukemia complications in the control group was significantly lower (4%) than that in the depressive group, which had an overall incidence of 24.21% ($P < 0.001$; Figure 2).

DISCUSSION

Previous studies have shown that the incidence of cancer-related fatigue in patients with malignant tumors ranges from 75% to 99%[7]. Patients with different types of malignant hematological diseases have high rates of cancer-related fatigue, but there are variations in the severity of cancer-related fatigue, suggesting that the type of hematological disease may influence the degree of cancer-related fatigue. Research has indicated that patients with depression experience dysregulation of autonomic nervous system function and neurotransmitter secretion in the brain[8]. This leads to decreased secretion of neurotransmitters such as dopamine and serotonin; increased levels of inflammatory mediators such as IL-1, IL-6, and TNF-α; and the induction of physical fatigue symptoms and various physiological discomforts. When the body experiences fatigue, negative emotions such as low mood, decreased interest, and even loss of interest are more likely to occur, causing leukemia patients to lose motivation for medical activities and daily life, thereby exacerbating fatigue. Depression and fatigue interact with each other, forming a vicious cycle. Studies have shown that psychological interventions such as mindful breathing, integrated psychological care, and diverse nursing can increase patients' potential, improve their compliance with medical advice and treatment, alleviate depression and anxiety, and reduce the severity of fatigue[9]. Therefore, in the clinical nursing process, it is necessary to detect patients' negative emotions early, assess their depressive state, and provide effective nursing interventions to alleviate depression and improve cancer-related fatigue in patients with malignant hematological diseases.

Based on the research in this article and the analysis of domestic and global studies, advanced age, concurrent radiotherapy, pain, and low hemoglobin levels are risk factors for cancer-related fatigue, while regular exercise acts as a protective factor. As elderly patients age, they experience organ aging, reduced stress tolerance, decreased immune function, and gradual physical weakness and are more susceptible to adverse symptoms caused by primary blood disorders and chemotherapy. Compared to younger individuals, their self-regulation abilities are weaker, resulting in more severe and longer-lasting cancer-related fatigue. Uslu and Canbolat[10] conducted a survey of 228 elderly cancer patients using the Edmonton Symptom Assessment System and the Cancer Fatigue Scale, recognizing age as a key risk factor influencing cancer-related fatigue. Therefore, it is crucial in nursing practice to have a real-time understanding of

Table 4 Multivariate regression analysis of piper fatigue scale scores in patients with malignant hematological diseases

	Value	B	SE	β	*t* value	*P* value
Age (years)		6.660	2.331	0.062	2.821	0.002[a]
Concurrent radiotherapy	(No = 1, Yes = 2)	123.09	69.894	0.042	2.021	0.033[a]
Regular exercise	(No = 1, Yes = 2)	-236.85	75.913	-0.068	-3.120	0.002[a]
Pain	Score	2.014	0.421	0.102	4.420	< 0.001[a]
Hemoglobin		2.825	1.333	0.043	2.081	0.031[a]

[a]$P < 0.05$.

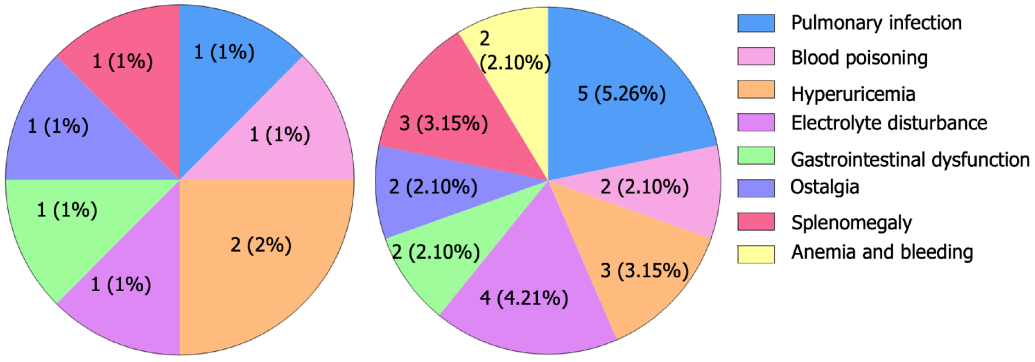

Figure 2 Comparison of leukemia complications between the two groups.

the physical condition of elderly patients, promptly identify their weakness and fatigue, and take proactive and effective intervention measures.

During the process of radiotherapy, all cells in the irradiated area are typically affected. Sensitive blood cells and tissue cells may undergo rapid division, leading to significant metabolic changes and stress responses in the body. This can cause adverse reactions in the surrounding tissues or throughout the body, such as ulcers, radiation dermatitis, and fatigue. It is crucial to address the negative emotions of radiotherapy patients and provide targeted psychological care to alleviate cancer-related fatigue symptoms and improve their quality of life[11].

Additionally, low hemoglobin levels are a risk factor for the severity of cancer-related fatigue. Hemoglobin is a functional protein in the blood that transports oxygen throughout the body. When hemoglobin levels decrease, the oxygen content in the blood also decreases, resulting in tissue hypoxia and subsequent fatigue symptoms[12]. Due to severe impairment of hematopoietic function in patients with hematologic malignancies, the number of red blood cells decreases, leading to reduced oxygen content in the blood and more pronounced fatigue. Therefore, in clinical interventions, it is necessary to improve the diagnosis and treatment of the underlying disease and improve the patient's hemoglobin levels. Under the guidance of doctors, health care professionals can provide patients with scientific dietary recommendations, increase their intake of iron, folate, vitamin B12, and other nutrients, and avoid consuming coffee, tea, and other substances that may hinder nutrient absorption. These measures can help improve a patient's nutritional status, alleviate cancer-related anemia, and relieve cancer-related fatigue[13].

Furthermore, subthreshold depressive states can exacerbate a patient's perception of pain. Previous research[14] has shown that depressive states increase sensitivity to pain and intensify the experience of pain. Leukemia patients often experience physical discomfort and pain. In this study, multivariate regression analysis with the inclusion of subthreshold depressive patients revealed pain as a risk factor for cancer-related fatigue, especially in later follow-up investigations where the incidence of bone pain complications was significantly higher in the depressive group than in the control group. Depressive states may make it more challenging for patients to tolerate pain, leading to increased fatigue and decreased quality of life.

This study indicated that regular exercise acts as a protective factor against cancer-related fatigue in patients with subthreshold depression. There is a strong correlation between exercise and the severity of cancer-related fatigue, and exercise is a crucial factor in determining the occurrence rate and severity of cancer-related fatigue. Regular exercise can alleviate cancer-related fatigue. Numerous intervention studies and meta-analyses have confirmed that aerobic exercise can reduce pain, tension, and depression caused by chemotherapy, improve cardiorespiratory endurance, enhance muscle strength, and improve overall health[15]. Multiple cancer-related guidelines recommend that patients with malignant tumors, under appropriate physical conditions, engage in moderate-intensity aerobic exercise or resistance training to alleviate cancer-related fatigue[16-18]. Therefore, it is suggested that health care professionals, in collaboration with patients' family members, provide guidance and supervision for leukemia patients to engage in personalized exercise choices such as running, fitness classes, swimming, and resistance training to prevent and alleviate cancer-related

fatigue. Furthermore, a follow-up survey conducted after discharge revealed that the overall complication rate in the control group was 4%, which was significantly lower than the 24.21% rate in the depressive group ($P < 0.001$). The occurrence of depression not only affects the symptoms of cancer-related fatigue but also has a significant impact on the prognosis and complications of patients.

CONCLUSION

In summary, the incidence of cancer-related fatigue in leukemia patients with comorbid subthreshold depression is as high as 92%. Age, concurrent radiotherapy, regular exercise, depression, and hemoglobin levels are factors influencing cancer-related fatigue. In clinical practice, it is crucial to pay close attention to the symptoms of cancer-related fatigue in advanced-aged patients, those receiving concurrent radiotherapy, patients with depression, and those with low hemoglobin levels. Early implementation of personalized intervention measures is highly important for preventing and alleviating the occurrence and development of cancer-related fatigue in patients with hematological malignancies.

FOOTNOTES

Author contributions: Liu YX initiated the project, designed the experiment and conducted clinical data collection, and performed postoperative follow-up and recorded data; Wang J conducted a number of collation and statistical analysis, and wrote the original manuscript; both authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Identifying relevant factors influencing cancer-related fatigue in patients with diffuse large B-cell lymphoma during chemotherapy

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Abstract

BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is a rapidly growing malignant tumor, and chemotherapy is one of the treatments used to combat it. Although advancements of science and technology have resulted in more and more patients being able to receive effective treatment, they still face side effects such as fatigue and weakness. It is important to thoroughly investigate the factors that contribute to cancer-related fatigue (CRF) during chemotherapy.

AIM

To explore the factors related to CRF, anxiety, depression, and mindfulness levels in patients with DLBCL during chemotherapy.

METHODS

General information was collected from the electronic medical records of eligible patients. Sleep quality and mindfulness level scores in patients with DLBCL during chemotherapy were evaluated by the Pittsburgh Sleep Quality Index and Five Facet Mindfulness Questionnaire-Short Form. The Piper Fatigue Scale was used to evaluate the CRF status. The Self-Rating Anxiety Scale and Self-Rating Depression Scale were used to evaluate anxiety and depression status. Univariate analysis and multivariate regression analysis were used to investigate the factors related to CRF.

RESULTS

The overall average CRF level in 62 patients with DLBCL during chemotherapy was 5.74 ± 2.51. In 25 patients, the highest rate of mild fatigue was in the cognitive dimension (40.32%), and in 35 patients the highest moderate fatigue rate in the behavioral dimension (56.45%). In the emotional dimension, severe fatigue had the highest rate of occurrence, 34 cases or 29.03%. The CRF score was positively correlated with cancer experience (all $P < 0.01$) and negatively correlated with cancer treatment efficacy (all $P < 0.01$). Tumor staging, chemotherapy cycle, self-

efficacy level, and anxiety and depression level were related to CRF in patients with DLBCL during chemotherapy.

CONCLUSION

There was a significant correlation between CRF and perceptual control level in patients. Tumor staging, chemotherapy cycle, self-efficacy level, and anxiety and depression level influenced CRF in patients with DLBCL during chemotherapy.

Key Words: Diffuse large B-cell lymphoma; Chemotherapy; Cancer-related fatigue; Anxiety; Depression; Mindfulness

Core Tip: The study aimed to explore the factors related to cancer-related fatigue (CRF), anxiety, depression, and mindfulness level in patients with diffuse large B-cell lymphoma (DLBCL) during chemotherapy. Univariate analysis and multivariate regression analysis were used to investigate the related factors of CRF. The overall average level of CRF in 62 patients with DLBCL during chemotherapy was 5.74 ± 2.51. There was a significant correlation between CRF and perceptual control level in patients with DLBCL during chemotherapy. Tumor staging, chemotherapy cycle, self-efficacy level, and anxiety and depression level influenced CRF in patients with DLBCL during chemotherapy.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL). DLBCL is characterized by progressive destruction of lymphoid structures or diffuse infiltration of large B lymphoid cells[1]. It is the most common NHL in adults, accounting for 30%-40% of all new cases. The cause of the disease is related to genes, the environment, viruses, and the aging population[2]. In 2020, 544352 new cases of NHL were reported worldwide, which ranked it as the 13th most common malignant tumor[3]. The incidence of DLBCL has increased worldwide in recent decades, including in China[4].

The molecular genetics and immunophenotype of DLBCL are highly heterogeneous, and chemotherapy is the primary clinical treatment[5]. However, the prolonged treatment cycle, high cost, and frequent adverse reactions associated with chemotherapy, along with patient concerns related to illness, can lead to prolonged periods of anxiety and depression. Cancer symptoms and the side effects of chemotherapy drugs make patients prone to negative emotions, fatigue, and other adverse reactions[6]. Cancer-related fatigue (CRF) is a common symptom in patients with DLBCL[7]. It is complex, and if severe it may affect quality of life, activities of daily life, and ultimately, survival. Fatigue is seldom an isolated condition and is typically accompanied by sleep disorders, unhealthy sleeping habits, emotional conditions (like depression and anxiety), or pain[8]. CRF usually lasts for a long time. It may begin at diagnosis and continue until several years after the end of treatment[9]. CRF and emotional disorders may be more uncomfortable for patients than symptoms like nausea, vomiting, and pain, which can be controlled by drugs[10]. Continuous CRF and emotional disorders not only affect quality of life and lead to delay or termination of antitumor therapy but also make patients unable to return to work and a normal life after curative treatment[11]. These destructive emotions seriously impact the effectiveness of treatment and quality of life and place a heavy burden on the patient's family. Thus, it is important to identify the variables that impact CRF, anxiety, and depression in DLBCL patients undergoing chemotherapy, from a clinical standpoint. That was the aim of this study.

MATERIALS AND METHODS

Study design and patients

We evaluated the data of 62 patients who were. diagnosed with DLBCL and admitted to the Fourth Hospital of Hebei Medical University between January 2020 and December 2022. The Ethics Committee of the Fourth Hospital of Hebei Medical University approved the study (No. 2020ky022) and it was performed following the ethical guidelines of the Declaration of Helsinki. All participants signed a written informed consent form.

Eligible patients were ≥ 20 years of age with DLBCL and symptoms of CRF and emotional disorders. All had been treated with similar chemotherapy regimens. Patients with any of the following were excluded: (1) Functional injuries of the heart, liver, lung, and other organs; (2) A previous history of mental illness or mental disorders; (3) Cognitive impairment; or (4) Incomplete clinical records or lack of follow-up.

Data collection

The clinical data of eligible patients, including sex, age, marital status, education level, disease diagnosis, tumor type, chemotherapy cycle, and family history, among others, were collected from their electronic medical records. During the course of radiotherapy, nursing staff evaluated the patient's fatigue and psychological state.

Diagnostic criteria of CRF

The CRF status of the patients was evaluated with the Chinese edition of the Piper Fatigue Scale (PFS)[12]. The PFS is a subjective self-evaluation scale of perceived fatigue. It comprises 27 items across four behavioral dimensions, namely behavioral (six items), emotional (five items), cognitive (six items), and perceptual (five items). Each item uses a 0-10 score scale. The score for each item represents the severity of fatigue, 0-3 for no or mild fatigue, 3-6 for moderate fatigue, and 6-10 for severe fatigue.

Evaluation of anxiety and depression

The Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS)[13] were used to evaluate the anxiety and depression status of patients. The SDS scale includes 20 items related to depression, with a score of 1-4 for each item. The higher the score, the more serious the item. The total score multiplied by 1.25 is converted into a percentile, and a total score > 53 indicated depression. The SAS scale includes 20 anxiety-related items, scoring 1-4 for each item. The higher the score, the more serious the item. The total score multiplied by 1.25 was converted into a percentile, and a total score > 50 indicated anxiety.

Evaluation of mindfulness awareness and sleep quality

The Chinese edition of the Five Facet Mindfulness Questionnaire-Short Form (FFMQ-SF)[14] was used to assess the mindfulness awareness level, which encompasses awareness, description, conscious action, nonjudgment, and nonreaction. Each dimension contains four items, each was scored from 1-5 points, and the total score is 20-100 points. The higher the score, the higher the level of mindfulness awareness. Sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI)[15]. The total PSQI score ranges from 0-21. The higher the score, the worse the sleep quality.

Evaluation of perceptual control

The Chinese version of the cancer experience and efficacy scale (CEES)[16] was used to evaluate the perceptual control ability of patients. The scale consists of two subscales, experience and efficacy, and each subscale includes three dimensions. The experience subscale is divided into personal experience (4 items), social experience (6 items), and emotional experience (6 items). The efficacy subscale is divided into individual efficacy (5 items), collective efficacy (5 items), and medical effectiveness (3 items). A total of 29 items are scored on a Likert scale, with responses ranging from "strongly disagree" to "strongly agree" with corresponding scores of 0 to 5. A high experience score indicates a more significant negative cancer experience. A high efficacy score indicates more effective dealing with cancer.

Statistical analysis

Continuous variables were reported as means ± SD or medians and interquartile range. Between-group differences were compared using the Mann-Whitney *U* test. Categorical variables are reported as *n* (%) and were compared using the χ^2 test or Fisher's exact test. Cox regression analysis was used to analyze the factors related to CRF in patients with NHL. $P < 0.05$ was regarded as statistically significant.

RESULTS

General patient information

Between January 2020 and December 2022, 662 DLBCL patients were treated in our department, and 304 were not enrolled because they did not meet the inclusion criteria. Of those, 86 were less than 18 years of age; 149 were excluded because they refused to participate, and 61 were excluded because of incomplete data. The remaining 62 participants were eligible and were included in the study analysis (Figure 1). Table 1 shows the demographic and clinical characteristics of the eligible patients.

Psychological symptoms of patients with DLBCL during chemotherapy

As shown in Table 2, the incidence of psychological symptoms in the 62 patients during chemotherapy was the highest for restless sleep (93.55%), followed by sadness (91.94%), forgetfulness (80.65%), distress (93.55%), and numbness (48.39%). The psychological symptom scores are shown in Figure 2A.

Sleep quality and mindfulness level scores in patients with DLBCL during chemotherapy

The sleep quality and mindfulness level scores during chemotherapy were evaluated by the PSQI and FFMQ-SF. The results are shown in Table 3.

CRF status of patients with DLBCL during chemotherapy

The CRF status of these 62 patients with DLBCL was investigated based on data from their electronic medical records

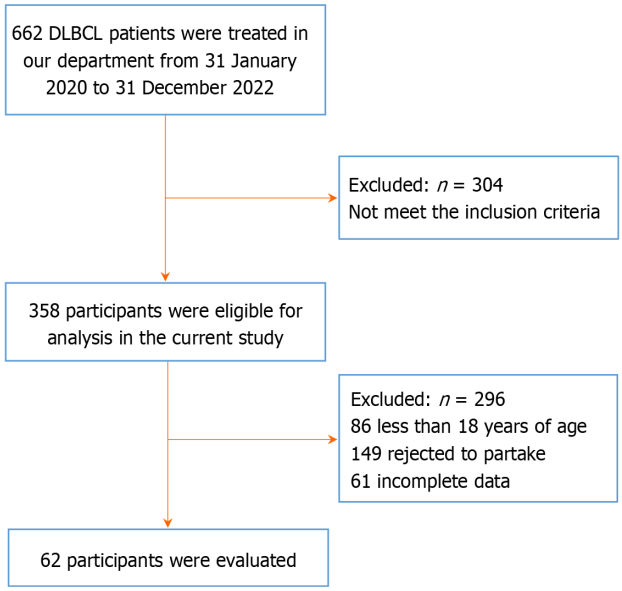

Figure 1 Flow diagram of the selection of study participants. DLBCL: Diffuse large B-cell lymphoma.

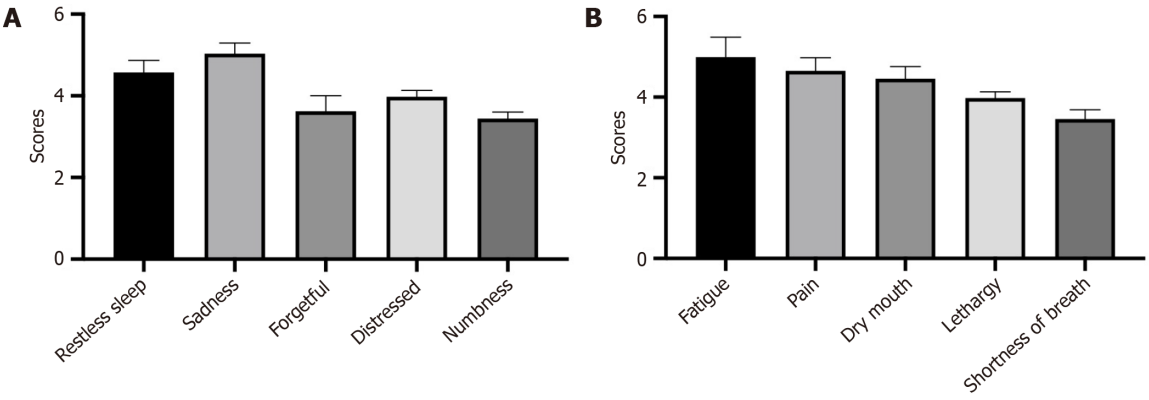

Figure 2 Psychological symptom scores and cancer-related fatigue-related symptom scores during chemotherapy. A: Psychological symptom scores during chemotherapy; B: Cancer-related fatigue-related symptom scores during chemotherapy.

(Table 4). The results showed that during chemotherapy the overall average CRF was 5.74 ± 2.51. In 25 patients (40.32%) the highest rate of mild fatigue was in the cognitive dimension, in 35 patients (56.45%). the highest rate of moderate fatigue was in the behavioral dimension, and in 34 patients (29.03%) the highest rate of severe fatigue was in the emotional dimension.

Univariate analysis of CRF in patients with DLBCL during chemotherapy

Univariate analysis was conducted to evaluate the factors related to CRF in patients with DLBCL. The results showed that pain, tumor stage, degree of anxiety and depression, chemotherapy cycle, and self-efficacy affected CRF in these patients during chemotherapy (all $P < 0.05$, Table 5).

CRF-related symptoms of patients with DLBCL during chemotherapy

As shown in Table 6, the incidence of CRF-related symptoms in these 62 patients was fatigue (95.16%), pain (82.26%), dry mouth (88.71%), lethargy (87.10%), and shortness of breath (45.16%). The symptom scores are shown in Figure 2B.

Perceptual control scores of patients with DLBCL during chemotherapy

The perceptual control scores of the 62 study patients are shown in Table 7.

Correlation analysis between CRF and perceptual control

The correlation between CRF and perceptual control in patients with DLBCL during chemotherapy is shown in Figure 3. The CRF score was positively correlated with cancer experience (all $P < 0.01$) and negatively correlated with cancer treatment efficacy (all $P < 0.01$).

Table 1 Demographic and clinical characteristics of study-eligible patients

Characteristics	Eligible, *n* = 62
Sex	
Male	29
Female	33
Age in years	
≤ 65	49
> 65	13
Education	
High school or less	23
College	20
Bachelor's degree	15
Graduate degree	4
ECOG performance status	
< 2	8
≥ 2	7
BMI in kg/m^2, median (IQR)	25.4 (22.2-28.7)
High serum LDH	9
High serum β2m	11

BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; LDH: Lactate dehydrogenase; β2m: β2-microglobulin.

Table 2 Psychological symptom scores in patients with diffuse large B-cell lymphoma during chemotherapy

Item	Eligible, *n* = 62	Score
Restless sleep	58 (93.55)	4.51 ± 1.38
Sadness	57 (91.94)	4.77 ± 1.40
Forgetfulness	50 (80.65)	3.48 ± 1.12
Distress	58 (93.55)	4.53 ± 1.37
Numbness	30 (48.39)	3.47 ± 1.08

Data are *n* (%).

Table 3 Pittsburgh Sleep Quality Index and Five-Facet Mindfulness Questionnaire-Short Form of patients with diffuse large B-cell lymphoma during chemotherapy

Assessment measure	Scores
PSQI	10.49 ± 1.28
FFMQ-SF	49.85 ± 10.67

PSQI: Pittsburgh Sleep Quality Index; FFMQ-SF: Five-Facet Mindfulness Questionnaire-Short Form.

Factors influencing CRF in patients with DLBCL during chemotherapy

As shown in Table 8, tumor stage, chemotherapy cycle, self-efficacy level, and anxiety and depression level were related to CRF in patients with DLBCL during chemotherapy.

Table 4 Cancer-related fatigue status of patients with diffuse large B-cell lymphoma, *n* = 62

Dimension	Average score	Mild fatigue, *n* (%)	Moderate fatigue, *n* (%)	Severe fatigue, *n* (%)
Behavior fatigue	6.57 ± 2.43	18 (29.03)	35 (56.45)	9 (14.52)
Emotional fatigue	5.25 ± 2.14	15 (24.19)	29 (46.78)	34 (29.03)
Perceived fatigue	6.39 ± 2.36	20 (32.26)	32 (51.61)	10 (16.13)
Cognitive fatigue	5.37 ± 2.48	25 (40.32)	21 (33.87)	16 (25.81)
Total CRF score	5.74 ± 2.51	24 (38.71)	26 (41.94)	12 (19.35)

CRF: Cancer-related fatigue.

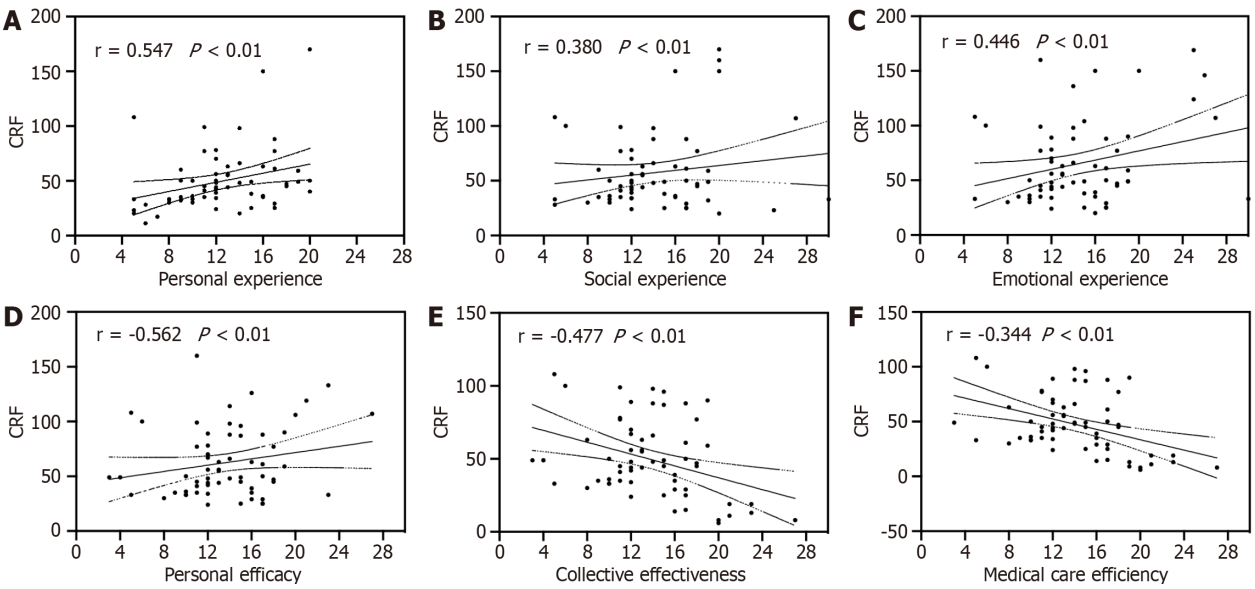

Figure 3 Correlation analysis between cancer-related fatigue and features of perceptual control in patients with diffuse large B-cell lymphoma during chemotherapy. A: Personal experience; B: Social experience; C: Emotional experience; D: Personal efficacy; E: Collective effectiveness; F: Medical care efficiency. CRF: Cancer-related fatigue.

DISCUSSION

CRF is a subjective feeling of lack of passion, weakness, lack of concentration, and a tendency to feel tired[17]. CRF is the most common symptom in cancer treatment, and its duration and intensity vary from person to person. Along with experiencing a significant decrease in physical strength, patients with CRF also have other negative symptoms, such as disinterest in their surroundings or self-doubt. These symptoms not only impact their daily lives but also pose a significant threat to their rehabilitation and overall quality of life[18]. This study focused on factors that influence CRF, anxiety, and depression in patients with DLBCL during chemotherapy because our understanding is currently limited and inconclusive.

Chemotherapy is the primary treatment for DLBCL. However, chemotherapy drugs may also kill normal cells. The occurrence of CRF during chemotherapy aggravates patients' negative emotions, which is not conducive to improving quality of life[19]. Most DLBCL patients have sleep disorders during chemotherapy, which may result from negative emotions surrounding the disease and the side effects of chemotherapy[20]. In This study investigated the status of CRF in patients with DLBCL. We observed that the overall average level of CRF in 62 patients with DLBCL during chemotherapy was 5.74 ± 2.51, of which 25 patients had the highest rate of mild fatigue in the cognitive dimension, and 35 patients had the highest moderate fatigue rate in the behavioral dimension. In the emotional dimension, the rate of severe fatigue was the highest in 34 cases. Therefore, it is of great significance to improve patients' cognitive level of fatigue and propose positive and effective measures to improve the degree of fatigue, promote their physical recovery, and improve their quality of life.

Patients with DLBCL must endure pain and discomfort caused by malignant tumors as well as adverse reactions caused by long-term chemotherapy[21]. Additionally, hospitalization can lead to a disruption of interpersonal communication and a sense of isolation, which often result in negative emotions such as anxiety and depression[22]. Previous studies have confirmed that alleviating negative emotions, such as tension, anxiety, and depression, and improving social and family psychological support reduced fatigue and improved their quality of life[23]. In addition,

Table 5 Univariate analysis of cancer-related fatigue in patients with diffuse large B-cell lymphoma

Influencing factors	Eligible, *n* = 62	Average PFS score	*P* value
Sex			0.543
Male	29	5.44 ± 2.32	
Female	33	5.74 ± 2.20	
Age in years			0.095
≤ 65	49	4.59 ± 1.25	
> 65	13	5.15 ± 2.42	
Marital status			0.206
Married	21	5.57 ± 2.34	
Unmarried	40	5.95 ± 2.53	
Others	1	6.54 ± 2.32	
Education			0.390
High school or less	23	4.39 ± 1.60	
College	20	4.37 ± 1.38	
Bachelor's degree	15	5.07 ± 2.21	
Graduate degree	4	5.93 ± 2.52	
Self-efficacy level	26		0.031
High	26	4.66 ± 1.71	
Medium	9	5.56 ± 2.30	
Low		5.90 ± 2.51	
Anxiety and depression degree			0.033
Mild	20	4.72 ± 1.32	
Moderate	29	5.50 ± 2.53	
Severe	13	5.97 ± 2.85	
Tumor staging			0.001
Stage I	25	4.34 ± 1.55	
Stage II	14	5.64 ± 2.19	
Stage III	13	5.82 ± 2.44	
Stage IV	10	6.78 ± 3.13	
Chemotherapy cycle			0.006
First cycle	23	4.09 ± 1.13	
Second cycle	19	4.52 ± 1.40	
Third cycle	11	5.72 ± 2.37	
Fourth cycle	9	6.46 ± 3.50	
Pain degree			0.004
Mild	15	4.54 ± 1.75	
Moderate	37	5.48 ± 2.44	
Severe	10	6.31 ± 3.47	

patients with advanced-stage disease may face increased mental stress and worry about the effectiveness of cancer treatment and their prognosis, which aggravates CRF[24]. Our study found that the severity of CRF in patients with DLBCL during chemotherapy in a state of depression and anxiety was significantly higher than it was in patients without depression and anxiety. The level of depression and anxiety significantly influenced CRF. The reason may be that patients with depression and anxiety are in a state of depression and slow thinking for a long time and are more likely to feel

Table 6 Cancer-related fatigue-related symptoms during chemotherapy in the study patients

Items	Eligible, *n* = 62	Score
Fatigue	59 (95.16)	4.48 ± 1.47
Pain	51 (82.26)	4.42 ± 1.48
Dry mouth	55 (88.71)	4.35 ± 1.32
Lethargy	54 (87.10)	4.08 ± 1.34
Shortness of breath	28 (45.16)	3.52 ± 1.16

Data are *n* (%).

Table 7 Perceptual control scores in patients with diffuse large B-cell lymphoma during chemotherapy

Items	Score
Cancer experience	
Personal experience	13.71 ± 1.98
Social experience	24.01 ± 3.02
Emotional experience	21.51 ± 3.12
Cancer efficacy	
Personal efficacy	15.71 ± 4.66
Collective efficacy	18.28 ± 4.72
Medical care efficacy	11.63 ± 2.03

Table 8 Factors influencing cancer-related fatigue in patients with diffuse large B-cell lymphoma during chemotherapy

Factor	Regression coefficient	Wald χ^2 value	*P* value	OR
Tumor staging	0.459	5.440	0.015	1.583
Chemotherapy cycle	0.233	4.629	0.003	1.339
Self-efficacy level	0.559	8.429	0.004	1.274
Anxiety and depression level	0.460	8.340	0.001	1.674

OR: Odds ratio.

tired. Furthermore, antidepressants such as mirtazapine and paroxetine have side effects that make patients tired and sleepy, which might also aggravate CRF.

The results of this study indicate that the CRF score was positively correlated with the cancer experience score in patients with DLBCL during chemotherapy. The reasons might be as follows. The higher the score of the cancer experience, the more serious the hostile experience of patients during chemotherapy, and patients with CRF often experience fatigue in behavior, emotion, feeling, and cognition. Patients experience physical fatigue and weakness that leave them unable to carry out daily tasks, worsening their negative personal, social, and emotional wellbeing, and leading to an increased cancer experience score. Furthermore, we found that the CRF score was negatively correlated with cancer treatment effectiveness in these 62 patients with DLBCL. The reasons might be as follows. Higher cancer treatment efficacy scores reflect stronger belief in disease control, and a more optimistic perception of cancer. Patients with high personal efficacy scores have more vital personal management ability, a more robust ability to control their experience of the disease, better psychological adjustment and self-care, and a reduced degree of CRF.

Our results demonstrated that clinical stage significantly influenced CRF in this group of patients The reasons might be as follows. Patients with advanced-stage disease have lymph node metastasis and distant metastasis, resulting in more severe symptoms of fatigue. As the disease progresses, tumors may invade more organs and tissues, causing damage to multiple systems in the body. This not only increases the complexity of treatment but may also lead to more severe fatigue symptoms[25]. Patients with advanced DLBCL may have more comorbidities and complications, which can themselves lead to fatigue and worsen during chemotherapy. Additionally, the diagnosis and treatment of advanced cancer can have a negative impact on a patient's mental state, resulting in anxiety, depression, and pessimism, which are

known risk factors of CRF[26]. Therefore, managing CRF in patients with clinically advanced DLBCL requires a comprehensive approach that includes symptom alleviation strategies, psychological support, rehabilitation training, and measures to improve quality of life. Healthcare professionals should be aware of the seriousness of CRF and consider this important issue in planning treatment to improve patient quality of life and treatment satisfaction.

The study has some limitations. Firstly, the sample size was small. Further research is warranted to validate and expand upon these findings, incorporating larger and more diverse patient populations. Furthermore, the study design might not have accounted for all potential confounding variables that could have influenced the results. Future research should consider controlling for these factors to ensure more accurate and reliable conclusions. Lastly, the findings of this study may be limited by the specific timeframe in which the data was collected. Future research should consider using objective measures to validate the findings.

CONCLUSION

In summary, tumor staging, chemotherapy cycle, self-efficacy level, and anxiety and depression levels were factors related to CRF in patients with DLBCL during chemotherapy. In the clinic, it is necessary to make reasonable treatment and nursing plans for patients with DLBCL combined with the clinical characteristics of CRF to improve their clinical symptoms, treatment effectiveness, and survival rate.

FOOTNOTES

Author contributions: Hao XQ and Qi Y initiated the project; Yang XD designed the experiment and conducted clinical data collection; Qi Y performed postoperative follow-up and recorded data; Hao XQ and Qi Y conducted a number of collation and statistical analysis and wrote the original manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (No. 2020ky022) and abided by the ethical guidelines of the Declaration of Helsinki.

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ORIGINAL ARTICLE

Retrospective Study

High-risk factors for delirium in severely ill patients and the application of emotional nursing combined with pain nursing

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Abstract

BACKGROUND

Delirium is a neuropsychiatric syndrome characterized by acute disturbances of consciousness with rapid onset, rapid progression, obvious fluctuations, and preventable, reversible, and other characteristics. Patients with delirium in the intensive care unit (ICU) are often missed or misdiagnosed and do not receive adequate attention.

AIM

To analyze the risk factors for delirium in ICU patients and explore the application of emotional nursing with pain nursing in the management of delirium.

METHODS

General data of 301 critically ill patients were retrospectively collected, including histories (cardiovascular and cerebrovascular diseases, hypertension, smoking, alcoholism, and diabetes), age, sex, diagnosis, whether surgery was performed, and patient origin (emergency/clinic). Additionally, the duration of sedation, Richmond Agitation Sedation Scale score, combined emotional and pain care, ven-tilator use duration, vasoactive drug use, drainage tube retention, ICU stay duration, C-reactive protein, procalcitonin, white blood cell count, body temperature, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and Sequential Organ Failure Assessment score were recorded within 24 h after ICU admission. Patients were assessed for delirium according to confusion assessment method for the ICU, and univariate and multivariate logistic regression analyses were performed to identify the risk factors for delirium in the patients.

RESULTS

Univariate logistic regression analysis was performed on the 24 potential risk factors associated with delirium in ICU patients. The results showed that 16 risk

factors were closely related to delirium, including combined emotional and pain care, history of diabetes, and patient origin. Multivariate logistic regression analysis revealed that no combined emotional and pain care, history of diabetes, emergency source, surgery, long stay in the ICU, smoking history, and high APACHE II score were independent risk factors for de-lirium in ICU patients.

CONCLUSION
Patients with diabetes and/or smoking history, postoperative patients, patients with a high APACHE II score, and those with emergency ICU admission need emotional and pain care, flexible visiting modes, and early intervention to reduce delirium incidence.

Key Words: Critical illness; Delirium; Risk factor; Intensive care unit; Emotional nursing; Pain nursing

Core Tip: Delirium incidence in intensive care unit (ICU) patients remains high and seriously affects their prognosis. To reduce the incidence of delirium in ICU patients, medical staff should be fully aware of delirium in critically ill patients and intervene it promptly. Medical staff should focus on the influence of combined emotional and pain care on delirium occurrence and establish individualized flexible visitation modes according to the patient's situation. We found that history of diabetes, smoking history, emergency referral to the ICU, surgery, long stay in the ICU, and high Acute Physiology and Chronic Health Evaluation II score were identified to be risk factors for delirium in critically ill patients.

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INTRODUCTION

Delirium, also known as acute brain syndrome, is characterized by disorientation, recent memory loss, and attention deficits. Delirious individuals have difficulty focusing, maintaining, or shifting their attention. These symptoms appear suddenly within a few hours or days[1]. These conditions fluctuate throughout the day and usually worsen at night (known as sunset phenomenon)[2]. These symptoms are short in duration and rarely last for more than a month. Delirium is not a disease but a clinical syndrome caused by a variety of factors. As a transient state of confusion caused by many factors, delirium manifests as a disturbance of consciousness and changes in cognitive function, with mental symptoms being the major manifestation[3]. The level of consciousness of patients with delirium varies, and the content of consciousness is disorganized, which is the result of the joint action of systemic disease and brain function. Delirium is often reversible and can appear within a few hours or days. Various factors are associated with delirium, such as medication, environment, and disease status. Comatose patients may experience delirium before regaining consciousness. Delirium can be divided into excitatory, inhibitory, and mixed types[4-6]. Excitatory delirium is characterized by agitation, restlessness, and attempts to remove tubes. Depressive delirium is characterized by apathy, impaired speech, and lethargy. The mixed type is typical of manifestations of both the above two types. The proportions of different sub-types of delirium in patients with severe disease vary significantly. Delirium is usually a sign of serious illness[7,8], with the cause being often an underlying condition. Delirium can be very serious, and around 15%-40% of hospitalized patients with delirium die within a month. Therefore, timely identification and treatment of delirium are extremely important[9]. A delirious person, if found untreated, should be immediately referred to a hospital. Treatment should be the first priority if another illness is found to be associated with delirium. Medications that could have potentially caused delirium should be discontinued. Approximately 35% of patients with delirium in the intensive care unit (ICU) are missed or misdiagnosed, and most patients do not receive adequate attention and corresponding management or treatment[10,11].

Emotional nursing, primarily through the language, expression, posture, attitude, behavior, and temperament of the nursing staff, affects and improves patients' mood, and relieves their concerns and troubles, so as to enhance their will and confidence to overcome the disease and reduce or eliminate the pain caused by various bad emotions and behaviors [12,13]. The various physical symptoms caused by these factors allow patients to receive treatment and care in the best psychological state to achieve early recovery. Patients with severe patients have a complex, changeable, and relatively high risk. Most patients experience a series of bad moods and poor sleep quality due to concerns about disease development, family economic burden, and pain. In routine nursing, clinical nurses often simply pursue of the execution of medical orders but ignore the mental health of patients. In recent years, holistic nursing has received increasing attention. In the current nursing system, psychological nursing has become an indispensable link in basic nursing, particularly in the context of emotional nursing[14-16].

This study conducted a regression analysis to screen out the risk factors that affect the occurrence of delirium to provide data support for clinical staff to identify the risk factors for delirium in critically ill patients early and take effective measures to manage delirium in time. The influence of emotional nursing combined with pain nursing on delirium was also examined.

MATERIALS AND METHODS

This retrospective study was approved by the ethics committee of Fourth Affiliated Hospital of Soochow University (Suzhou Dushu Lake Hospital, China). All the patients signed an informed consent form before inclusion in the study.

Patient recruitment and selection criteria

We enrolled patients who were referred to or admitted to our emergency ICU because of serious illness between December 2020 and June 2023. The inclusion criteria were as follows: (1) Met the relevant diagnostic criteria in "Intensive Care Specialist Nursing"; (2) Age ≥ 18 years; (3) ICU retention time ≥ 24 h; and (4) Non-cardiac surgery patients. The exclusion criteria were: (1) Combined with spiritual illness; (2) Patients that remained in coma after admission to ICU; and (3) There was hearing impairment.

Study design

This was a retrospective study in which critically ill patients admitted to the emergency ICU of the Fourth Affiliated Hospital of Soochow University between January 1, 2020 and December 30, 2023 were selected.

The main contents of emotional nursing include: (1) Relaxing mentality: Providing patients with a comfortable environment and reducing the impact of environmental stimuli such as noise; (2) Empathy: Understanding the patient's personal preferences, maintaining communication with the patient, and avoiding excessive attention to the disease; and (3) Emotional guidance: Establishing a good nurse-patient relationship, channeling patients' bad emotions, and reducing their psychological burden.

The main measures of pain care include: (1) Pain care: The information of the patient's previous pain duration and pain degree was collected to provide reference for subsequent analgesia measures. When the pain occurred, the patients were instructed to distract their attention by listening to music, reading books or newspapers, *etc.* And the patients were taught to relax. Massage, hot compress, and other measures can also be used to help patients relieve pain; and (2) Diet and daily life guidance: If the degree of pain was mild after surgery, the patient would be instructed to take oral compound vitamin B and other drugs to assist pain relief. At the same time, the patient was instructed to exercise.

Clinical variable selection

Based on the results of several systematic reviews at home and abroad, data related to delirium in ICU patients were selected for analysis. Data were collected using an electronic medical record information system and patient medical records. The finally included factors were as follows: (1) General information: Sex, age, smoking history, hypertension history, diabetes history, and heart disease history; (2) Disease factors: Acute physiology and chronic health evaluation II (APACHE II) score, GCS score, infection, respiratory failure, hypoxemia, *etc.* The APACHE II and GCS scores were evaluated within 24 h after admission to the ICU; (3) Treatment factors: Surgery, invasive mechanical ventilation, length of stay, sedatives, glucocorticoids; and (4) Laboratory indicators: White blood cell count, procalcitonin, C-reactive protein, albumin, acid-base imbalance, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, *etc.*

Delirium assessment

The degree of sedation and consciousness was assessed using the Richmond Agitation Sedation Scale (RASS) score. Patients were then assessed for delirium according to the confusion assessment method for the ICU (CAM-ICU), a combination of timing and situational modalities, twice a day (8:00 and 20:00). All patients were screened and assessed for delirium using the CAM-ICU, while delirium was assessed and recorded at any time as the patient's ideology changed. RASS, CAM-ICU, and APACHE II scores were used to evaluate delirium.

Statistical analysis

Statistical analyses were performed using Prism software (version 7.0). Measurement data are expressed as the mean ± SD, and comparison of data conforming to a normal distribution was performed using the t test. Count data are expressed as percentages (%) and were compared using the χ^2 test. The risk factors for delirium were determined *via* univariate and multivariate logistic regression analyses, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 301 patients were included in the study, including 184 men and 117 women, with an average age of (64.73 ± 16.03) years. Emergency source accounted for 48.84% of the 147 cases. The sources of the department were general

surgery (n = 188), oncology (n = 46), obstetrics and gynecology (n = 5), general medicine (n = 30), and orthopedic surgery (n = 32).

Factors affecting delirium

As presented in Table 1, combined emotional and pain care, history of diabetes, smoking, alcoholism, renal insufficiency, use of vasoactive drugs, indentured drainage tube, patient origin (emergency/outpatient), surgery, ventilator use time, ICU admission time, C-reactive protein level within 24 h of ICU admission, APACHE II score, Sequential Organ Failure Assessment score, sedative use time, and RASS score were significantly associated with delirium (P < 0.05), while age, sex, hypertension, heart disease, body temperature, white blood cell count, and calcium intake had no significant association with delirium (P > 0.05).

Table 1 Univariate analysis of risk factors for delirium in intensive care unit patients, *n* (%)

Variable	Delirium group (n = 102)	Non-delirium group (n = 199)	χ^2/t	P value
Combined emotional and pain care	42 (41.18)	108 (54.27)	4.625	0.032
Diabetes history	37 (36.27)	39 (19.60)	9.937	0.002
Patient source (emergency)	75 (73.53)	72 (36.18)	37.650	< 0.001
Surgery	80 (78.43)	183 (91.96)	11.190	0.001
Smoking history	59 (57.84)	62 (31.16)	19.980	< 0.001
Alcoholism history	35 (34.31)	38 (19.10)	8.501	0.004
Renal insufficiency	39 (38.24)	19 (9.55)	35.680	< 0.001
Use of vasoactive drugs	78 (76.47)	82 (41.21)	33.680	< 0.001
Placement of an indwelling drainage tube	101 (99.02)	180 (90.45)	7.465	0.006
Ventilator time (h)	70.85 ± 7.01	20.33 ± 1.70	9.068	< 0.001
ICU stay (d)	6.23 ± 0.52	2.07 ± 0.14	9.834	< 0.001
C-reactive protein level (mg/L)	165.70 ± 10.14	123.20 ± 7.82	3.364	< 0.001
Length of sedative medication (h)	56.67 ± 5.56	17.01 ± 1.08	9.218	< 0.001
APACHE II score	16.42 ± 0.36	12.19 ± 0.26	9.439	< 0.001
SOFA score	6.81 ± 0.28	4.55 ± 0.18	7.124	< 0.001
RASS score	-3.86 ± 0.04	-3.72 ± 0.05	2.011	0.045

ICU: Intensive care unit; APACHE: Acute Physiology and Chronic Health status assessment; SOFA: Sequential Organ Failure Assessment; RASS: Richmond Agitation Sedation Scale.

Multivariate logistic regression analysis

Table 2 presents the results of the multivariate analysis. Combined emotional and pain care, smoking history, emergency surgery, emergency transfer to ICU, surgery, long stay in ICU, and high APACHE II score were identified to be independent risk factors for delirium in critically ill patients (P < 0.05).

Effect of combined emotional and pain care on incidence of delirium

Multivariate logistic regression analysis showed that the risk of delirium in critically ill patients who received combined emotional and pain care was only 1/3 of that in patients who did not. A total of 301 patients were included in this study. Among the 151 patients who did not use emotional nursing and pain nursing, 60 developed delirium, with an incidence of 39.74%; among the 150 patients who received combined emotional and pain nursing, 42 developed delirium, with an incidence of 28.00%. The incidence of delirium in patients receiving emotional nursing combined with pain nursing was significantly lower than those not receiving (χ^2 = 0.59, P < 0.05). There was no significant difference in sex or age between the patients who received combined emotional and pain nursing and those who did not (P > 0.05), as shown in Table 3.

DISCUSSION

In this study, logistic regression analysis was performed on the risk factors that may affect delirium in ICU patients, and it was found that no use of combined emotional and pain care, history of diabetes, history of smoking, emergency admission, surgery, long stay in the ICU, and high APACHE II score were associated with delirium in ICU patients.

Table 2 Multivariate analysis of risk factors for delirium in intensive care unit patients

Variable	OR	95%CI	*P* value
Combined emotional and pain care	0.351	0.146-0.845	0.020
Diabetes history	4.631	1.787-11.999	0.002
Patient source (emergency)	0.308	0.118-0.802	0.016
Surgery	6.250	1.459-26.772	0.014
ICU stay	1.659	1.240-2.219	0.001
Smoking history	2.787	1.094-7.100	0.032
APACHE II score	1.421	1.246-1.621	< 0.001

95%CI: 95% confidence interval; OR: Odds ratio; ICU: Intensive care unit; APACHE: Acute Physiology and Chronic Health status assessment.

Table 3 Comparison of clinical data and incidence of delirium between patients with and without combined emotional and pain care, *n* (%)

Characteristics	Patients with combined emotional and pain care (*n* = 150)	Patients without combined emotional and pain care (*n* = 151)	χ^2	*P* value
Age			0.033	0.855
< 65 years	86 (57.3)	85 (56.3)		
≥ 65 years	64 (42.7)	66 (43.7)		
Sex			2.506	0.113
Male	85 (56.7)	99 (65.6)		
Female	65 (43.3)	52 (34.4)		
Delirium			4.625	0.032
Yes	65 (43.3)	60 (39.7)		
No	108 (72.0)	91 (60.3)		

This study further analyzed four important factors: Combined emotional and pain care, emergency transfer, ICU stay time, and diabetes history. Previous studies have suggested that the duration and frequency of combined emotional and pain care in ICU patients may affect the occurrence of delirium[17-19]. To date, no domestic study has reported the effects of combined emotional and pain care on delirium in ICU patients. This study found that the incidence of delirium in critically ill patients without combined emotional and pain care was 3.5 times higher than that of patients receiving combined emotional and pain care. Compared to ordinary wards, the closed management mode of the ICU brings patients separated anxiety, and combined emotional and pain care can bring patients a certain sense of security and comfort. Combined emotional and pain care can alleviate patients' negative emotions during treatment and play a role in protecting the body under stress. These results suggest that in addition that the medical staff needs to master sufficient theoretical knowledge and practical skills, the nursing model is also an essential and important factor for the prevention of delirium in ICU patients. It is important that medical personnel should establish a more scientific and humanized detection mode according to the individual needs of the patients.

This study also found that the risk of delirium in patients undergoing emergency surgery was three times higher than that of patients not undergoing. Compared to those who were not transferred to the emergency room, patients who were transferred to the emergency room experienced fast, rapidly changing, and intense mental stimulation. Lack of sufficient preoperative communication, such as pain, body constraints, and vision systems, can cause intense fear and anxiety. Negative emotions can induce various stressful reactions and increase the incidence of delirious errors[20]. Therefore, medical staff should strengthen psychological care for patients who are transferred to the ICC to prevent and reduce the incidence of delirium in the early stages of psychological intervention, thereby decreasing the psychological stress response of the patient after admission to the ICU.

Owing to the particularity of ICU work needs, ICU patients are often disturbed by various sounds, lights, and treatment measures, making awake patients unable to ensure normal effective sleep. Studies have shown that sleep disorders are closely related to the occurrence of delirium in ICU patients[21,22]. In this study, the probability of delirium increased by 1.659 times (OR = 1.659) for each additional day of ICU stay. This suggests that medical staff should pay more attention to patients who need to stay in the ICU for a long time because of their illness, especially to ensure effective sleep of patients at night, reduce the stimulation of sound and light on patients, centralize treatment measures

under the premise of ensuring patient safety, and improve patients' sleep by using earplugs and eye masks, and listening to soothing music. If necessary, drugs should be administered to assist sleep according to the patient's condition.

The results of this study also suggest that the risk of developing delirium in patients with diabetes is approximately 4.6 times that of patients without. Diabetes can damage the cardiovascular system; patients who have been ill for many years often experience varying degrees of cerebrovascular and nerve damage, resulting in poor concentration and memory loss [22,23]. In the clinical work of ICU, the evaluation and prevention of delirium in patients with diabetes should be strengthened, blood glucose changes should be closely monitored, hypoglycemic drugs should be used rationally, and irreversible damage to the cardiovascular and cerebrovascular system caused by hyperglycemia or hypoglycemia should be avoided.

There are certain limitations in this study. The sample size of this study is not large enough and it is a single-center study, so the results are not sufficiently responsive to the real world and the results are not highly universal. High-quality randomized controlled studies are needed to support these results.

CONCLUSION

The incidence of delirium in ICU patients remains high and seriously affects their prognosis. To reduce the incidence of delirium in ICU patients, medical staff should be fully aware of delirium in critically ill patients and intervene it promptly. The results of this study suggest that medical staff should pay more attention to the influence of the nursing model on the occurrence of delirium in patients and establish individualized and flexible visitation modes according to the patient's situation. In addition, the results of this study show that a history of diabetes, smoking, emergency referral to the ICU, postoperative surgery, long stay in the ICU, and high APACHE II score are also risk factors for delirium in critically ill patients.

FOOTNOTES

Author contributions: Li HR designed the research study; Li HR and Guo Y performed the research; Li HR and Guo Y contributed new reagents and analytical tools; Li HR and Guo Y analyzed the data and wrote the manuscript; and all authors have read and approved the final version of the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Impact of early refined nursing program on prognosis of middle-aged and elderly patients with cognitive dysfunction combined with cerebral infarction

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Abstract

BACKGROUND

Cerebral infarction is a local or extensive necrosis of brain tissue. Subsequently, the corresponding neurological deficits appear. The incidence of cerebrovascular diseases in China is increasing gradually. After the onset of cerebrovascular disease, the most common sequelae include movement disorders, language disorders, and cognitive dysfunction.

AIM

To investigate the effect of early refined nursing program on the prognosis of middle-aged and elderly patients with cerebral infarction combined with cognitive dysfunction.

METHODS

A retrospective study was conducted to divide 60 patients with cerebral infarction and cognitive impairment into an experimental group (n = 32) and a control group (n = 28). The experimental group received early intensive care every day, and the control group received daily routine care. The scores of the Mini-Mental State Examination (MMSE) and the Trail Making Test (TMT), as well as the latency and amplitude of the event-related potential P300, were used as main indicators to evaluate changes in cognitive function, and changes in BDNF, TGF-β, and GDNF expression were used as secondary indicators.

RESULTS

Both groups experienced notable enhancements in MMSE scores, with the experimental group demonstrating higher scores than the control group (experimental: 28.75 ± 2.31; control: 25.84 ± 2.87). Moreover, reductions in TMT-A and TMT-B

scores were observed in both groups (experimental: TMT-A 52.36 ± 6.18, TMT-B 98.47 ± 10.23; control: TMT-A 61.48 ± 7.92, TMT-B 112.63 ± 12.55), with the experimental group displaying lower scores. P300 Latency decreased (experimental: 270.63 ms ± 14.28 ms; control: 285.72 ms ± 16.45 ms), while amplitude increased (experimental: 7.82 μV ± 1.05 μV; control: 6.35 μV ± 0.98 μV) significantly in both groups, with superior outcomes in the experimental cohort. Additionally, the levels of the growth factors BDNF, TGF-β1, and GDNF surged (experimental: BDNF 48.37 ng/mL ± 5.62 ng/mL, TGF-β1 52.14 pg/mL ± 4.28 pg/mL, GDNF 34.76 ng/mL ± 3.89 ng/mL; control: BDNF 42.58 ng/mL ± 4.73 ng/mL, TGF-β1 46.23 pg/mL ± 3.94 pg/mL, GDNF 30.25 ng/mL ± 2.98 ng/mL) in both groups, with higher levels in the experimental group.

CONCLUSION

For middle-aged and elderly patients with cerebral infarction and cognitive dysfunction, early refined nursing can significantly improve their cognitive function and prognosis.

Key Words: Early refined nursing program; Cerebral infraction; Cognitive impairment; Psychiatry; Trajectory test

Core Tip: The incidence of cerebrovascular diseases in China is increasing gradually. After the onset of cerebrovascular disease, the most common sequelae include movement disorders, language disorders, and cognitive dysfunction. Cognitive impairment in patients with cerebral infarction may or may not be accompanied by focal dysfunction, such as apraxia, agnosia, aphasia, memory impairment, and executive dysfunction. For middle-aged and elderly patients with cerebral infarction and cognitive dysfunction, early refined nursing can significantly improve their cognitive function and prognosis.

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INTRODUCTION

Cerebral infarction is a local or extensive necrosis of brain tissue. The blood-supplying vessels of the brain exhibit narrowing and occlusion of the lumen. This causes a sudden decrease in blood flow to the brain tissue, or no blood flow through it, resulting in ischemia and hypoxic necrosis of the brain tissue, followed by corresponding neurological deficit symptoms. The incidence of cerebrovascular diseases in China is gradually increasing. According to relevant epidemiological investigations and research, cerebrovascular diseases in China are increasing, with the mortality rate of cerebrovascular diseases ranking first among various causes of death, reaching as high as 22.45%[1]. After the onset of cerebrovascular disease, the most common sequelae include movement disorders, language disorders, and cognitive impairment.

Numerous studies have shown that survivors of acute ischemic stroke are prone to experiencing decreased levels of cognitive function. The probability of incidence within 3 mo after cerebral infarction is approximately 62.6%, and the long-term functional effects will persist[2,3]. In addition, studies have shown that after the onset of ischemic cerebrovascular disease, more than one-third of patients develop vascular cognitive impairment. In China, the incidence of vascular cognitive impairment in people aged over 60 years is 11.95%[4]. Studies have also conducted follow-ups on cerebral infarction patients and found that the incidence of cognitive impairment after one year reached 49.5%[5]. Cognitive impairment in patients with cerebral infarction may or may not be accompanied by focal functional impairments such as apraxia, agnosia, aphasia, memory impairment, and executive function impairment. Several studies have suggested that advanced age, long-term hypertension, diabetes, and hyperlipidemia can contribute to the occurrence and progression of cognitive impairment in patients with cerebral infarction. These factors are considered to be associated with an increased risk of vascular cognitive impairment[6]. Cognitive impairment has a significant impact on the ability to perform daily activities and engage in social life in patients with cerebral infarction, leading to a decrease in quality of life for these patients[7]. Additionally, cognitive impairment is associated with decreased adherence to treatment and medication, resulting in an impact on treatment efficacy. Furthermore, studies have indicated a higher mortality rate in patients with cerebral infarction who also have cognitive impairment[8]. Conventional models of nursing care are generally effective, but they may lack specificity in addressing individual patient needs. Therefore, it is crucial to explore more targeted and personalized interventions to enhance the effectiveness of nursing care.

The emergence of refined nursing interventions represents a paradigm shift in healthcare, offering a nuanced approach that integrates medical science with a humanistic perspective, addressing patients' physical, psychological, and social needs. Unlike traditional models, the refined nursing program is all-encompassing, spanning from admission to treatment completion. It involves meticulous tailoring of each aspect of care, guided by a patient-centered philosophy, promoting individualized and effective interventions. In contrast to conventional nursing practices, the refined approach

emphasizes early intervention, with specific considerations for the unique circumstances of each hospital. The nursing plans are meticulously designed based on the patient's disease type, research findings, surgical outcomes, and potential for functional rehabilitation. Notably, the emphasis on "patient-centered" care underscores the individuality of each patient, tailoring interventions to meet their specific needs. To exemplify the impact of refined nursing, a study by Shi W delved into the early implementation of refined nursing programs for middle-aged and elderly patients with cerebral infarction and cognitive impairment, particularly in the context of respiratory critical care[9].

MATERIALS AND METHODS

Population

Sixty patients with cerebral infarction and cognitive impairment were recruited from the Rehabilitation Medicine Department of Ganzhou People's Hospital, Jiangxi Province, China from January 2021 to September 2022. The Ethics Committee of Ganzhou People's Hospital approved the study (No. 200230107). Written consent was obtained from those who were eligible and willing to participate after admission to the Rehabilitation Medicine Department of Ganzhou People's Hospital.

The inclusion criteria for the participants were as follows: (1) First-time cerebral infarction that met the clinical diagnostic criteria[10] and was confirmed by brain computed tomography or magnetic resonance imaging, with stable vital signs; (2) being conscious and able to cooperate with relevant treatment; (3) having a Montreal Cognitive Assessment Scale score ≤ 24 points; (4) having a disease course of more than 1 mo; and (5) being aged 45-70 years old.

The exclusion criteria for patients were as follows: (1) Having cognitive dysfunction before onset; (2) having contraindications to high-frequency repetitive transcranial magnetic stimulation therapy; (3) having heart, liver, kidney, or other important organ insufficiency; (4) having a history of cerebral hemorrhage, epilepsy, or brain trauma; (5) having a history of alcohol or drug dependence before the onset of this illness; and (6) deterioration of the condition and appearance of a new infarction lesion.

Intervention methods

In the control group, routine nursing measures were used, the patients' vital signs were closely monitored, nursing assessments were implemented, and medication guidance and health education were provided for 12 wk.

The experimental group received a refined nursing program based on conventional nursing. This primarily involved giving attention and care to patients with cerebral infarction, actively communicating with them, alleviating their tension through positive emotions, soft language, and comforting measures, and providing scientific explanations about their illness.

The refined nursing program for patients with cerebral infarction specifically focused on those in the acute stage. It primarily included timely admission to the intensive care unit (ICU) or other appropriate departments, minimizing waiting time in the emergency department, establishing an infusion channel, promptly administering oxygen and other necessary measures, and closely monitoring changes in the patients' condition according to first-level nursing standards. Additionally, efforts were made to minimize patient movements, including both the number and amplitude of such movements. At the same time, according to the sex and height of the cerebral infarction patient, the head of the bed should be appropriately raised, and the cleaning and care of the mouth, mucous membranes, skin, and vulva of patients with cerebral infarction should be strengthened.

According to the cognitive function of patients, a neuroprotective diet, including the Mediterranean diet, was provided, and the cessation of the diet triggered high blood pressure or increased the consumption of olive oil. Patients in the acute phase need no drinking water, need to use a gastric tube to inject nutritional supplements through nasal feeding, and can be assisted by a nasogastric pump when conditions permit.

Admission and critical care

Routine nursing care (control group): Patients in the control group received standard care, with no specific emphasis on timely admission to specialized units or critical care measures.

Refined nursing program (experimental group): The refined program prioritized timely admission to the ICU or suitable departments, minimized wait times, and ensured prompt administration of oxygen and other necessary measures following first-level nursing standards.

Psychological and emotional support

Routine nursing care (control group): Standard care included general psychological support but lacked a structured approach to alleviate tension through positive emotions, soft language, and comforting measures.

Refined nursing program (experimental group): Actively engaging with patients, the refined program aimed to establish a strong nurse-patient relationship, reduce psychological burdens, and enhance patient confidence through tailored emotional care.

Personalized dietary care

Routine nursing care (control group): Dietary care in the control group was generally standard, without specific consideration for cognitive function or a neuroprotective diet.

Refined nursing program (experimental group): Tailored meal care included providing a neuroprotective diet, such as the Mediterranean diet, and adjusting diets based on cognitive function, avoiding triggers for high blood pressure.

Complication management

Routine nursing care (control group): Standard procedures were followed, without specific adjustments to air conditioning parameters or detailed observations of urine output and color.

Refined nursing program (experimental group): The program included meticulous complication management, with adjustments to air conditioning parameters, maintenance of an optimal environment, and detailed observation and guidance on urine output and water intake.

Encouragement of physical activity

Routine nursing care (control group): Exercise was generally encouraged without specific emphasis on early-stage exercise or the principle of "step by step."

Refined nursing program (experimental group): Actively encouraging early-stage exercise, the refined program followed the principle of "step by step," promoting exercise in the company of family members or nursing workers.

In summary, the refined nursing program demonstrated a comprehensive and tailored approach, addressing not only the physical but also the psychological and environmental needs of patients, particularly those in the acute stage of cerebral infarction. The control group, in contrast, received standard care without the specific refinements outlined in the experimental group's program.

Cognitive outcome parameters

Primary indicators included the scores of the Mini-Mental State Examination (MMSE)[11] and the Trail Making Test (TMT), as well as the latency and amplitude of the event-related potential P300. The P300 Latency and amplitude were measured using an electromyography/evoked potential instrument.

Secondary indicators were changes in growth factors including BDNF, TGF-β1, and GDNF, and they were utilized to assess changes in cognitive function at 0, 6, and 12 wk after the start of the intervention. BDNF, TGF-β1, and GDNF were measured *via* enzyme-linked immunoassay after venous blood collection.

Statistical analysis

SPSS 24.0 was used for all statistical analyses. After conducting the Kolmogorov-Smirnov test, continuous variables that followed a normal distribution are presented as the mean ± SD. For intergroup analysis, the independent sample *t* test was used. Moreover, repeated-measures ANOVA was used for intergroup analysis. Discontinuous variables that did not conform to a normal distribution are expressed as percentages, and nonparametric tests were used for intergroup analysis. Statistical significance was set at $P < 0.05$.

RESULTS

Baseline patient information

A total of 60 patients with cerebral infarction and cognitive impairment were enrolled in the study. The average age of the patients was 59.64 ± 4.13 years, and the average body mass index (BMI) was 24.47 ± 3.45 kg/m^2. Among the participants, 58.33% were male and 41.67% were female. A total of 41.67% of the patients had a history of smoking, and 18.33% had a history of drinking. Moreover, 66.67% of the patients had an education level below junior high school, 21.67% had a high school education background, and 11.66% had an education level above university. Additionally, 61.67% of the patients had left-sided infarctions, while 38.33% had right-sided infarctions. Furthermore, 11.66% of the patients had a history of coronary heart disease, and 11.66% had a history of atrial fibrillation.

There were no significant differences observed between the two groups regarding age, sex, BMI, lesion side, educational background, history of hypertension, history of coronary heart disease, or history of atrial fibrillation ($P > 0.05$; Table 1).

Changes in MMSE and TMT scores

The differences in the intergroup comparison, time comparison, and intergroup time interactive comparison of MMSE and TMT-A scores between the two groups were statistically significant ($P < 0.05$). Similarly, for the TMT-B scores, the differences in the intergroup comparison and the time comparison between the two groups were statistically significant ($P < 0.05$), while the difference in the intergroup time interaction comparison was not statistically significant ($P > 0.05$). At 6 wk and 12 wk, both groups exhibited higher MMSE scores compared to their respective scores at 0 wk, whereas the scores of TMT-A and TMT-B were lower than those at 0 wk in both groups. These differences were statistically significant ($P < 0.05$). Furthermore, the MMSE scores in the experimental group were greater than those of the control group, and the TMT-A and TMT-B scores were lower than those of the control group. These differences were also statistically significant ($P < 0.05$; Table 2).

Table 1 Comparison of demographic data between the two groups, *n* (%)/mean ± SD

Item	Experimental group (*n* = 32)	Control group (*n* = 28)	$t/\chi^2/Z$	*P* value
Age (yr)	59.45 ± 3.94	59.87 ± 4.40	0.390	0.697
Gender			0.765	0.381
Man	17 (53.13)	18 (64.29)		
Woman	15 (46.87)	10 (35.71)		
BMI (kg/m²)	24.88 ± 3.62	24.01 ± 3.27	0.971	0.335
Smoking history	13 (40.63)	12 (42.85)	0.030	0.861
Drinking history	5 (15.62)	6 (21.42)	0.335	0.561
Side of lesion			2.116	0.145
Left side	17 (53.13)	20 (71.43)		
Right side	15 (46.87)	8 (28.57)		
Education background			1.558	0.119
Junior high school and below	24 (75.00)	16 (57.14)		
Senior high school	6 (18.75)	7 (25.00)		
College and above	2 (6.25)	5 (17.86)		
History of hypertension	23 (71.87)	19 (67.85)	0.114	0.734
History of coronary heart disease	4 (12.50)	3 (10.71)	0.035	0.850
History of atrial fibrillation	5 (15.62)	2 (7.14)	0.381	0.536

Table 2 Changes in Mini-Mental State Examination and Trail Making Test scores, mean ± SD

Item	Time (wk)	Experimental group (*n* = 32)	Control group (*n* = 28)	Inter-group comparison (*F*/*P* value)	Time comparison (*F*/*P* value)	Inter-group time interactive comparison (*F*/*P* value)
MMSE score	0	18.45 ± 3.52	18.84 ± 4.74	9.451/0.002	37.030/< 0.001	4.395/0.013
	6	21.69 ± 3.24[a,b]	19.32 ± 3.05[b]			
	12	25.26 ± 2.38[a,b]	22.12 ± 2.19[b]			
TMT-A score	0	82.35 ± 12.84	81.66 ± 14.57	9.016/0.003	193.200/< 0.001	3.664/0.027
	6	61.58 ± 10.25[a,b]	71.34 ± 11.46[b]			
	12	41.59 ± 5.32[a,b]	46.75 ± 5.87[b]			
TMT-B score	0	162.18 ± 45.25	163.36 ± 42.16	5.332/0.022	57.420/< 0.001	1.151/0.318
	6	123.73 ± 23.11[a,b]	141.39 ± 22.96[b]			
	12	96.76 ± 16.33[a,b]	109.42 ± 19.86[b]			

[a]*P* < 0.05 compared with control group.
[b]*P* < 0.05 compared with 0 wk.
MMSE: Mini-Mental State Scale; TMT: Trail Making Test.

Changes in P300

The differences in the intergroup comparison and the time comparison of the P300 Latency and amplitude between the two groups were statistically significant ($P < 0.05$). However, the difference in the intergroup time interaction coefficient was not statistically significant ($P > 0.05$). At 6 and 12 wk, the P300 Latency in both groups was shorter than that at 0 wk within the same group. Additionally, the amplitude of the P300 was greater than that at 0 wk within the same group. These differences were statistically significant ($P < 0.05$). Moreover, the latency of P300 in the experimental group was lower than that of the control group, and the amplitude was greater than that of the control group. These differences were also statistically significant ($P < 0.05$; Table 3).

Table 3 Changes in the latency and amplitude of P300, mean ± SD

Group	Latency (ms)			Amplitude (μv)		
	0 wk	6 wk	12 wk	0 wk	6 wk	12 wk
Experimental group (n = 32)	452.38 ± 40.52	402.31 ± 21.14[a,b]	365 ± 15.13[a,b]	4.53 ± 2.14	6.18 ± 1.74[a,b]	6.89 ± 1.45[a,b]
Control group (n = 28)	467.84 ± 43.99	437.79 ± 22.57[b]	384.23 ± 16.46[b]	4.41 ± 2.08	5.22 ± 1.93[b]	6.02 ± 1.66[b]
Inter-group comparison (F/P value)	30.340/< 0.001			5.556/0.019		
Time comparison (F/P value)	136.700/< 0.001			17.600/< 0.001		
Inter-group time interactive comparison (F/P value)	2.179/0.116			0.932/0.395		

[a]P < 0.05 compared with control group.
[b]P < 0.05 compared with 0 wk.

Changes in growth factors

The differences in the intergroup comparison, time comparison, and intergroup time interactive comparison of BDNF, TGF-β1, and GDNF levels between the two groups were statistically significant (P < 0.05). At 6 wk and 12 wk, the levels of BDNF, TGF-β1, and GDNF in both groups were greater than those at 0 wk within the same group. Furthermore, the experimental group exhibited higher levels of BDNF, TGF-β1, and GDNF than did the control group. These differences were statistically significant (P < 0.05; Table 4).

DISCUSSION

In this study, after 6 and 12 wk of intervention, the experimental group exhibited higher scores on the MMSE, P300 amplitude, BDNF, TGF-β1, and GDNF than the control group. Moreover, the experimental group showed lower scores on the Trail Making Test parts A and B (TMT-A and TMT-B) and P300 Latency than the control group. These differences were statistically significant (P < 0.05). These results suggest that the refined nursing model has a more pronounced impact on cognitive function than the conventional nursing model.

Our findings are consistent with those of previous studies. P300, BDNF, TGF-β1, and GDNF are closely associated with cognitive function[10-14]. P300, which is not influenced by the characteristics of physical stimulation, is closely associated with cognitive function. The P300 Latency reflects the speed at which the brain recognizes and processes information, thereby providing an indication of the overall level of cognitive function to some extent[10,12]. BDNF is predominantly expressed by neurons in the central and peripheral nervous systems, particularly in the hippocampus. It plays a vital role in the growth and development of the nervous system, supporting neuron survival and promoting neurogenesis[11]. TGF-β1 is selectively expressed in specific brain regions, such as the hippocampus, cortex, meninges, and choroid plexus. It protects neurons from various forms of damage, including excitotoxicity, hypoxia, ischemia, and trophic factor deprivation[13]. GDNF is a significant growth factor for the development, survival, and maintenance of dopaminergic neurons in the midbrain. It also plays a crucial role in the proliferation, migration, and differentiation of nerve cells[14].

Various factors affecting the normal function and structure of the cerebral cortex can contribute to the development of cognitive impairment[15-18]. The incorporation of rich environmental stimuli in the refined nursing model can facilitate the enhancement of cognitive function by influencing the plasticity of the nervous system, including modifications in the thickness, severity, and volume of the hippocampus. These changes can also influence the levels of neurotransmitters such as dopamine, serotonin, and glutamate and promote the increased production of BDNF and VEGF, which are essential substances involved in shaping neuroplasticity[19]. Animal studies have consistently demonstrated that environmental enrichment can enhance cognitive abilities and improve behavior. For instance, rats exposed to enriched environments exhibit enhanced spatial and nonspatial memory compared to those raised in impoverished environments [20]. Additionally, research has indicated that environmental enrichment positively impacts the information processing ability of the hippocampus and has a beneficial effect on age-related cognitive impairment[21].

The efficacy of cognitive rehabilitation programs in improving cognitive function among stroke survivors has been well-documented[22]. Additionally, interventions aimed at promoting neuroplasticity, such as constraint-induced movement therapy, have shown promising results in stroke rehabilitation[23]. Furthermore, studies have highlighted the neuroprotective effects of growth factors, including BDNF, TGF-β1, and GDNF, in the context of stroke recovery[24]. Extending the findings of this study to broader clinical practice aligns with the principles of patient-centered care and evidence-based medicine. By integrating personalized interventions targeting cognitive function, neuroplasticity, and neuroprotection into routine clinical practice, healthcare providers can optimize treatment outcomes for cerebral infarction patients across diverse healthcare settings[25]. Moreover, collaborative efforts involving interdisciplinary healthcare teams, including neurologists, rehabilitation specialists, and nursing professionals, are essential for implementing and optimizing fine nursing care plans in clinical practice[26].

The results of this study provide potential value for implementing sophisticated care planning in clinical practice, particularly in other healthcare settings and patient populations. The observed improvements, such as increases in

Table 4 Changes in growth factors, mean ± SD

Item	Time (wk)	Experimental group (*n* = 32)	Control group (*n* = 28)	Inter-group comparison (*F*/*P* value)	Time comparison (*F*/*P* value)	Inter-group time interactive comparison (*F*/*P* value)
BNDF (ng/mL)	0	4.85 ± 0.79	4.92 ± 0.83	19.330/< 0.001	146.100/< 0.001	9.113/< 0.001
	6	6.63 ± 1.05[a,b]	6.07 ± 0.86[b]			
	12	8.77 ± 1.25[a,b]	7.28 ± 1.14[b]			
TGF-β1 (ng/L)	0	15.42 ± 2.54	15.68 ± 2.99	19.080/< 0.001	92.220/< 0.001	8.759/< 0.001
	6	20.44 ± 3.12[a,b]	18.56 ± 3.08[b]			
	12	25.71 ± 3.52[a,b]	21.13 ± 3.66[b]			
GDNF (pg/mL)	0	288.61 ± 25.26	282.74 ± 24.18	40.080/< 0.001	157.200/< 0.001	6.016/0.003
	6	346.59 ± 25.84[a,b]	312.72 ± 26.38[b]			
	12	392.27 ± 29.96[a,b]	355.06 ± 30.47[b]			

[a]*P* < 0.05 compared with control group.
[b]*P* < 0.05 compared with 0 wk.

cognitive function, neuroplasticity, and growth factor levels, provide strong support for comprehensive treatment options for patients with cerebral infarction. This intensive care plan can include personalized cognitive rehabilitation programs, neuroplasticity promotion measures, and growth factor treatments. By promoting this comprehensive treatment program to other medical institutions and patient groups, it is expected to improve the treatment effect for patients with cerebral infarction and reduce the impact of cognitive dysfunction and neurological damage on patients' quality of life. Therefore, this study provides valuable implications for broader clinical practice and treatment options in the future.

Nevertheless, there are a few limitations in this study. The inclusion of a limited number of participants and the use of a single-center study design may have introduced bias into the results. Additionally, the study participants were exclusively patients with cerebral infarction, which limits the generalizability of the findings to patients with cognitive impairment from other medical conditions. It is important to address these limitations by expanding the sample size, enhancing the study design, and conducting further analysis and discussion of the research results.

CONCLUSION

The early implementation of refined nursing programs holds significant promise for improving the cognitive function of middle-aged and elderly patients with cerebral infarction and cognitive impairment. These refined nursing programs encompass a multifaceted approach that integrates personalized cognitive rehabilitation strategies, neuroplasticity-promoting interventions, and targeted administration of growth factors. By initiating such interventions promptly following the onset of cerebral infarction, healthcare providers can capitalize on the brain's inherent capacity for adaptation and recovery, thereby maximizing treatment efficacy.

FOOTNOTES

Author contributions: Xiong HL designed and conducted this study; Lu X, Lu YH, and Zhong P completed the nursing process and data integration and analysis; Xiong HL completed the writing of the manuscript; Zhong P completed the review of the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Correlation of preoperative inflammatory factors and emotional disorders with postoperative delirium in patients with craniocerebral trauma

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Abstract

BACKGROUND

Traumatic brain injury (TBI) imposes a substantial societal and familial burden due to its high disability and fatality rates, rendering it a serious public health problem. Some patients with TBI have poor treatment outcomes and are prone to postoperative delirium (POD), which affects their quality of life. Anxiety has been linked to increased POD incidence in some studies, while others have found no correlation.

AIM

To investigate the correlation of POD risk factors, preoperative inflammatory factors, and mood disorders in patients with TBI.

METHODS

We retrospectively collected data on the treatment of 80 patients with TBI from November 2021 to September 2023. Patients were grouped as POD and non-POD, according to their POD status, and the general data of the two groups were compared. Inflammatory factor levels were detected preoperatively, and the Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) were used to investigate the risk factors associated with POD in these patients. Logistic regression was used to identify the independent risk factors.

RESULTS

Twenty-one patients (26.25%) developed POD, including 7, 10, and 4 cases of the excitatory, inhibitory, and mixed types, respectively. There were 59 cases (73.75%) in the non-POD group. Compared with the non-POD group, the POD group had a significantly higher proportion of patients with low Glasgow Coma Scale (GCS)

scores before admission, unilateral mydriasis, preoperative hemorrhagic shock, intraventricular hemorrhage (IVH), and postoperative hyperglycemic hyperosmolar disease ($P < 0.05$). In the POD group, interleukin-6 (IL-6), human tumor necrosis factor-α (TNF-α), myeloperoxidase levels, HAMA, and HAMD scores were higher than those in the non-POD group (all $P < 0.05$). Logistic multivariate analysis showed that GCS score at admission, IVH, IL-6, TNF-α, HAMA, and HAMD were independent risk factors for POD in patients with TBI ($P < 0.05$).

CONCLUSION

Low GCS score at admission, IVH, elevated IL-6 and TNF-α, other inflammatory indicators, anxiety, and depression, can increase the risk of POD in patients with TBI after surgery.

Key Words: Inflammatory factors; Mood disorders; Traumatic brain injury; Postoperative delirium; Relevance; Risk factor

Core Tip: Traumatic brain injury (TBI) is a common form of trauma caused by external violence, resulting in head and brain injuries. TBI ranks second only to limb injuries in all body regions. It is a complex and severe injury with high disability and mortality rates, often manifesting symptoms such as disturbed consciousness, neurological dysfunction, and increased intracranial pressure, posing significant risks to patient safety. This study examines the risk factors for postoperative delirium (POD) in patients with TBI, aiming to enable early intervention and reduce POD occurrence.

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INTRODUCTION

Traumatic brain injury (TBI), the most prevalent critical neurological condition, has a high mortality and disability rate, imposing significant burdens on society and families and posing substantial challenges to medical and health management[1]. Postoperative delirium (POD) is a common complication of TBI, characterized by fluctuations in consciousness, inattention, and confusion. POD usually occurs 2-5 days after surgery[2]. POD has a high incidence in patients with TBI, leading to long-term cognitive dysfunction, increased mortality risk, and significant impacts on patient prognosis[3]. Currently, there is no specific drug for treating POD, emphasizing the importance of early identification of high-risk patients. The etiology of POD includes various mechanisms, such as neuroinflammation, neurotransmitter imbalance, changes in biological rhythm, and changes in brain metabolism. Many studies have shown the crucial role of neuroinflammation in the onset and progression of POD[4-6]. In addition, psychiatric symptoms closely reflect the metabolism and function of the nervous system, serving as reliable indicators of POD onset and progression. Previous reports have indicated a significant association between anxiety and increased POD incidence, although some studies failed to establish a correlation between the two[7,8]. Therefore, this study examined the associated risk factors for POD in patients with TBI and investigated the correlation between preoperative inflammatory factors, emotional disorders, and POD in this population to provide a reference for the pathological mechanism and clinical treatment of patients with TBI.

MATERIALS AND METHODS

General information

Eighty patients with TBI treated at Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City) between November 2021 and September 2023 were included in the study.

Inclusion criteria included: Age > 18 years, a definite history of trauma, and trauma onset within 24 hours before admission.

Exclusion criteria were: Severe injury to other organs; the presence of hematological diseases, cancer, severe infections, autoimmune diseases, liver and kidney dysfunction; poor heart, lung, liver, and kidney function; inability to tolerate surgery or coagulation insufficiency caused by long-term use of antiplatelet or anticoagulant drugs; and death within 3 days after admission.

A postadmission computed tomography scan was required to confirm traumatic intracranial hematoma in all patients.

Diagnostic criteria for delirium

The patients were assessed by a trained physician using the confusion assessment method, which involves evaluating the following: (1) Acute changes in mental status; (2) Inattention; (3) Disorganized thinking; and (4) Change in consciousness level. Delirium is diagnosed if any one of the following conditions is met: (1) and (2), plus (3), or (4)[9]. Delirium can manifest in three types: Excited type: Increased activity, decreased ability to control activity, restlessness, and wandering; Inhibitory type: Decreased activity, slowed-down behavior, decreased ability for environmental recognition, reduced language quantity and speed, fatigue, and decreased arousal or autism; Mixed type: Alternating episodes of excitation and inhibition.

Assessments began on the first day after the completion of surgery and were performed once daily until the patient's discharge or death.

Inflammatory factor detection

On the morning after admission, 10 mL of fasting venous blood was collected from each patient after an 8-hour fasting period and placed in a sodium citrate anticoagulant blood collection tube. After 15 min of centrifugation in a 3000 r/min centrifuge, the supernatant was collected and stored at -20 °C until testing. Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels in the samples were measured by a radioimmunoassay (ELISA kit), while serum myeloperoxidase (MPO) levels were measured using an ultraviolet spectrophotometer.

Emotional disorder assessment

The Hamilton Depression Scale (HAMD, 17 items) was used to evaluate depression status and severity in patients with TBI before surgery. Scores on the scale range from 0-34 points, with a HAMD score ≥ 7 indicating depression[10]. Similarly, the Hamilton Anxiety Scale (HAMA, 14 items) was used to evaluate anxiety levels in patients with TBI. Scores on this scale range from 0-56 points, with a HAMA score ≥ 7 indicating anxiety[11].

Surgical methods

Surgical procedures were performed based on the location and volume of the hematoma. This involved making a surgical incision, cutting through the scalp and muscles layer-by-layer, drilling a hole, milling the skull to remove the epidural hematoma, cutting the dura to remove the subdural hematoma, and extracting the intracerebral hematoma under a microscope. During surgery, the decision to remove the bone flap was made by the two doctors based on consensus and the swelling of the brain tissue. For patients treated with decompressive craniectomy, a dural tension-relieving suture was placed, a drainage tube was inserted, and the muscle scalp was sutured layer-by-layer. Postoperative care included analgesia, sedation, fluid infusion, intensive care, anti-infection therapy, and rehabilitation.

Observational indicators

(1) General Information: Age, sex, body mass index (BMI), time from trauma to admission, Glasgow Coma Scale (GCS) score on admission, intracranial pressure on admission, pupil change, preoperative hemorrhagic shock, hematoma volume, midline shift, preoperative drilling and drainage, ventricular hemorrhage, basal cisterna compression, postoperative hyperglycemia, and hyperosmolality; (2) Inflammatory factors: IL-6, TNF-α, and MPO; and (3) Mood disorders: HAMD and HAMA scores.

Statistical analysis

SPSS 27.0 was used to analyze the data of the study patients. The measurement data were expressed as mean ± SD, and comparisons between the two groups were performed using independent sample *t*-tests. The rate of count data was expressed as percentages, and the chi-squared test was used for comparisons between groups. $P < 0.05$ was considered statistically significant. Logistic regression analysis was used to analyze the correlation between the study variables, with OR and 95%CI used to evaluate risk factors.

RESULTS

POD occurrence in patients with TBI

Among the 80 patients, 63 were male and 17 were female. Their ages ranged from 26 to 71 years, with a mean of 48.56 ± 8.62 years. A total of 21 patients (26.25%) developed POD, including seven cases of excitatory type, 10 cases of inhibitory type, and four cases of mixed type, while 59 cases (73.75%) were non-POD (Figure 1).

General data of patients with TBI

The proportion of patients with lower GCS scores before admission, unilateral mydriasis, preoperative hemorrhagic shock, intraventricular hemorrhage (IVH), postoperative hyperglycemia, and hyperosmolarity was higher in the POD group compared to the non-POD group ($P < 0.05$). Age, sex, BMI, time from trauma to admission, intracranial pressure on admission, pupil changes, hematoma volume, midline shift, and preoperative factors such as drilling and drainage and compression ring pool differences were not significant between the two groups ($P > 0.05$; Table 1).

Table 1 General data of patients with traumatic brain injury, mean ± SD/*n* (%)

Index	POD group (*n* = 21)	Non-POD group (*n* = 59)	χ^2/t	*P* value
Age (year)	50.48 ± 8.53	47.88 ± 8.62	1.188	0.239
Sex			0.111	0.738
Male	16 (76.19)	47 (79.66)		
Female	5 (23.81)	12 (20.34)		
BMI (kg/m^2)	22.08 ± 2.23	22.50 ± 2.76	0.631	0.530
Time from trauma to admission (minutes)	85.10 ± 15.51	83.39 ± 12.13	0.513	0.609
Admission GCS score (score)			7.770	0.005
≤ 3	10 (47.62)	10 (16.95)		
> 3	11 (52.38)	49 (83.05)		
Intracranial pressure at admission (mmHg)	52.95 ± 10.73	49.85 ± 10.73	1.139	0.258
Pupil changes			4.195	0.041
Single side scattered	7 (33.33)	35 (59.32)		
Bilateral scattered	14 (66.67)	24 (40.68)		
Prehemorrhagic shock			6.792	0.009
Yes	11 (52.38)	13 (22.03)		
No	10 (47.62)	46 (77.97)		
Hematoma volume (mL)	55.95 ± 12.36	53.49 ± 11.55	0.823	0.413
Midline shift			1.566	0.211
< 10 mm	7 (33.33)	29 (49.15)		
≥ 10 mm	14 (66.67)	30 (50.85)		
Preoperative drilling and drainage			0.007	0.934
Yes	18 (85.71)	52 (88.14)		
No	3 (14.29)	7 (11.86)		
Ventricular hemorrhage			3.975	0.046
Yes	7 (33.33)	8 (13.56)		
No	14 (66.67)	51 (86.44)		
Compressed ring pool			0.132	0.717
Compressed unilateral ring pool	9 (42.86)	28 (47.46)		
Compressed bilateral ring pool	12 (57.14)	31 (52.54)		
Postoperative high glucose hyperpermeability			8.366	0.004
Yes	8 (38.10)	6 (10.17)		
No	13 (61.90)	53 (89.83)		

POD: Postoperative delirium; BMI: Body mass index; GCS: Glasgow Coma Scale.

Preoperative inflammatory factor levels in patients with TBI

The IL-6 score was 21.62 ± 5.68, the TNF-α score was 65.71 ± 14.19, and the MPO score was 132.24 ± 17.01 in the POD group. IL-6, TNF-α, and MPO levels were higher in the POD group compared to the non-POD group (χ^2 = 4.105, 2.948, and 3.640, respectively, $P < 0.05$; Table 2).

Scores of anxiety and depression in the two groups

In the POD group, the HAMA score was 7.71 ± 2.80, and the HAMD score was 7.57 ± 2.34. Twelve patients (57.14%) had a HAMA score of 7, and 14 patients (66.67%) had a HAMD score of 7. In comparison, the HAMA score for the non-POD group was 5.86 ± 2.91, and the HAMD score was 4.98 ± 2.46. Twenty-one patients (35.59%) had a HAMA score of 7, and 13 patients had a HAMD score of 7. Compared to the non-POD group, the POD group had higher preoperative anxiety

Table 2 Preoperative levels of inflammatory factors in both groups, mean ± SD

Index	POD group (*n* = 21)	non-POD group (*n* = 59)	*t* value	*P* value
IL-6	21.62 ± 5.68	16.78 ± 4.22	4.105	< 0.05
TNF-α	65.71 ± 14.19	56.19 ± 12.18	2.948	0.004
MPO	132.24 ± 17.01	115.19 ± 18.09	3.640	< 0.05

POD: Postoperative delirium; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; MPO: Myeloperoxidase.

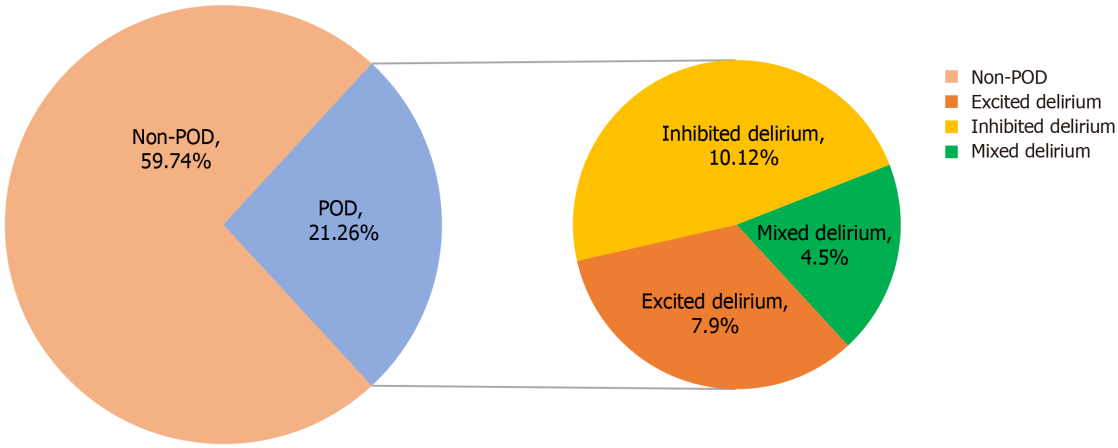

Figure 1 Development of postoperative delirium in patients with traumatic brain injury. POD: Postoperative delirium.

and depression ($P < 0.05$; Figure 2).

Multivariate Logistic regression analysis

The relevant univariate variables were included in the multivariate logistic regression analysis, and the variable assignments are presented in Table 3. The optimal cutoff values of IL-6, TNF-α, and MPO were determined to be 17.5, 64.5, and 132.5, respectively. The results indicated that admission GCS score, IVH, IL-6, TNF-α, HAMA, and HAMD were identified as risk factors for POD in patients with TBI ($P < 0.05$; Table 4).

DISCUSSION

As economic and transportation infrastructures develop rapidly, the incidence of TBI is increasing annually. TBI is characterized by severe conditions, rapid progression, and high disability and mortality rates, presenting significant challenges to neurologists[12]. Therefore, it is necessary to explore the prognostic factors affecting patients with TBI.

Relevant studies have highlighted that patients with TBI are prone to POD, which not only causes neurological impairment but also increases the risk of other complications, prolongs the length of hospital stay, and leads to adverse outcomes such as permanent cognitive impairment and death[13,14]. Reports indicate an overall incidence of POD of 23%, consistent with the 26.25% incidence observed in patients with TBI in our study and similar to previous studies[15,16]. Recent studies have shown that POD is caused by dysregulation of basal neuronal activity secondary to systemic disorders and is mainly associated with neuroinflammation[17]. Therefore, focusing on inflammatory factors and responses can help elucidate the risk factors associated with POD in patients with TBI, thereby promoting TBI treatment and improving patient prognosis.

This study's results showed that the proportion of patients with a low GCS score before admission, bilateral pupillary dilation, preoperative hemorrhagic shock, IVH, postoperative hyperglycemia, and hyperosmolarity was higher in the POD group compared to the non-POD group.

The GCS is the basic tool used to assess consciousness alterations in patients with TBI, with a score of 3-5 points indicating severe TBI. Patients with severe TBI experience rapid disease progression, severe secondary brain injury, significant treatment difficulty, high mortality rates, and severe disability rates, leading to traditionally low expectations for their treatment outcomes. This affects the patient's family and even impacts the confidence of neurosurgeons[18,19].

During the progression of TBI, changes in the patient's pupil are often indicative of the evolving condition. In healthy individuals, the pupil is symmetrical, round, centered, and possesses a smooth edge, with a diameter of approximately 2.5 mm-4.0 mm under diffuse natural light.

Table 3 Variable assignments

Index	Assignment
POD circumstances	1 = POD, 0 = non-POD
Admission GCS score	1 = ≤ 3, 0 = > 3
Pupil changes	1 = Bilateral scattered, 0 = Single side scattered
Prehemorrhagic shock	1 = yes, 0 = no
Ventricular hemorrhage	1 = yes, 0 = no
Postoperative high glucose hyperpermeability	1 = yes, 0 = no
IL-6	1 = ≥17.5, 0 = < 17.5
TNF-α	1 = ≥ 64.5, 0 = < 64.5
MPO	1 = ≥ 132.5, 0 = < 132.5
HAMA	1 = ≥ 7, 0 = < 7
HAMD	1 = ≥ 7, 0 = < 7

POD: Postoperative delirium; GCS: Glasgow Coma Scale; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; MPO: Myeloperoxidase; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale.

Table 4 Multivariate logistic regression analysis

Index	B	SE	Wald χ^2	*P* value	OR	95%CI
Admission GCS score	2.232	1.058	4.453	0.035	9.321	1.172-74.105
Pupil changes	1.060	0.955	1.230	0.267	2.886	0.444-18.770
Prehemorrhagic shock	1.365	1.109	1.516	0.218	3.918	0.446-34.444
Ventricular hemorrhage	2.878	1.151	6.249	0.012	17.777	1.862-169.742
Postoperative high glucose hyperpermeability	1.123	1.366	0.676	0.411	3.075	0.211-44.755
IL-6	2.538	1.104	5.291	0.021	12.659	1.456-110.082
TNF-α	2.344	1.062	4.867	0.027	10.421	1.299-83.616
MPO	0.713	1.108	0.414	0.520	2.039	0.233-17.887
HAMA	2.127	1.020	4.349	0.037	8.394	1.137-61.993
HAMD	2.421	1.081	5.011	0.025	11.256	1.352-93.735

GCS: Glasgow Coma Scale; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; MPO: Myeloperoxidase; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale.

Mydriasis occurs when the iris dilator muscle contracts, causing the pupil to dilate beyond 5 mm in diameter. Bilateral mydriasis indicates bilateral nerve damage, which is a serious consequence of increased intracranial pressure resulting from various diseases, such as cerebrovascular disease and encephalitis, leading to poor patient prognosis[20,21].

Patients with TBI are prone to developing hemorrhagic shock. During this state, tissue perfusion decreases, leading to cellular anaerobic metabolism, elevated lactic acid levels, and metabolic acidosis. If left untreated, this condition can lead to organ failure or even death[22]. Some studies have pointed out that massive parenchymal hemorrhage or intracranial hematoma may compress the ventricular system, leading to IVH[23]. IVH is a type of large-scale intracerebral hemorrhage, and is considered to be a dynamic process. The initial hemorrhage may develop immediately after the formation and expansion of an hematoma, leading to the expansion of edema in the surrounding brain tissue. After hematoma formation, the ventricles will fill up with blood" instead, which will cause different degrees of damage to the brain tissue of the patient. IVH will also lead to ischemia of the tissue surrounding the hematoma and cause secondary brain injury. In addition, IVH itself may aggravate brain tissue damage, further increase the risk of preoperative hemorrhagic shock and endangering the safety of the patient. The incidence of IVH in patients with traumatic injuries to the brain exceeds 30%, and the mortality rate is as high as 50%[24].

Patients with craniocerebral trauma often experience blood glucose elevation, peaking approximately 12-24 hours after injury and manifesting as a hyperglycemic hyperosmolar state. The primary mechanisms behind this phenomenon include nerve stimulation, damage to hormone-secreting structures such as the hypothalamus and pituitary gland, and

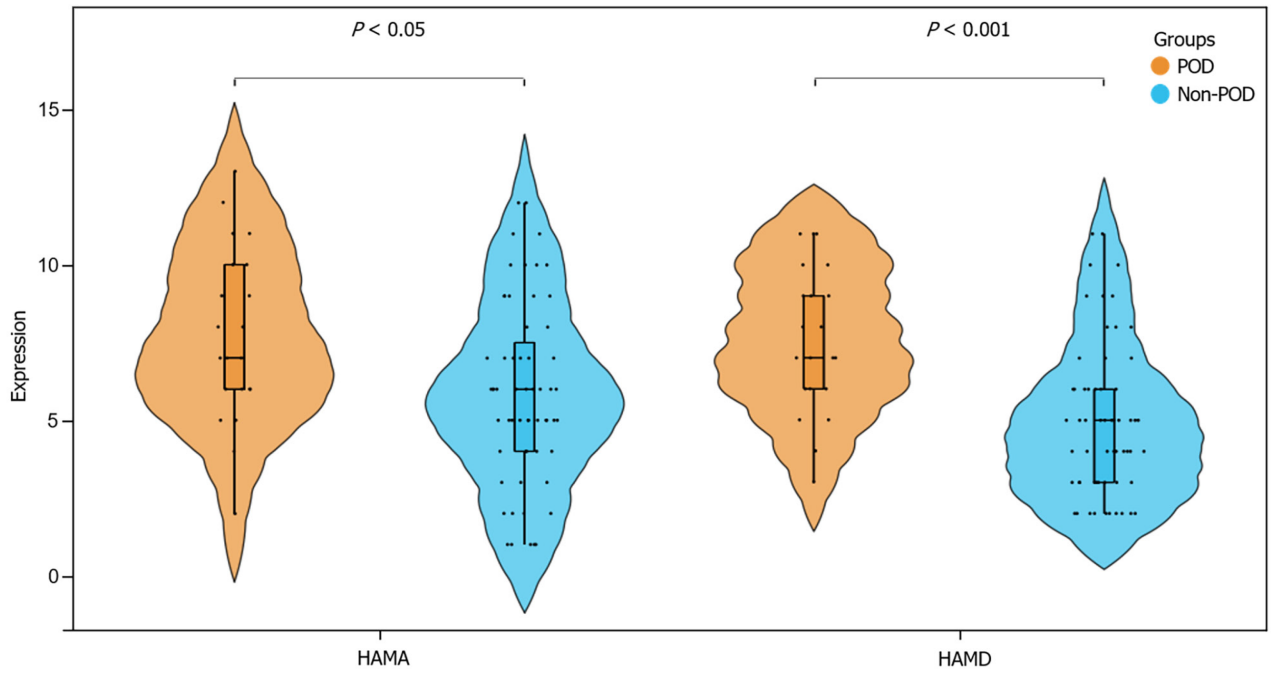

Figure 2 Anxiety and depression scores of the patients in both groups. POD: Postoperative delirium; HAMA: Hamilton depression scale; HAMD: Hamilton anxiety scale.

the body's stress response, resulting in increased secretion of glucagon, catecholamines, and glucocorticoids. Simultaneously, hyperglycemia and hyperosmicity can aggravate nerve damage through lactic acidosis, electrolyte imbalances, and hyperosmolar coma, leading to a poor patient prognosis[25].

In the multivariate analysis of this study, GCS scores at admission and IVH were identified as risk factors for POD in patients with TBI. Conversely, the *P* values of bilateral pupil dilation, preoperative hemorrhagic shock, postoperative hyperglycemia, and hyperosmolarity were greater than 0.05, which were largely related to insufficient sample size or sampling bias.

The neuroinflammation theory states that inflammatory mediators can compromise the blood-brain barrier, infiltrate the central nervous system, and prompt microglia to produce inflammatory factors that induce central neuronal and synaptic damage, eventually leading to neuroinflammation and POD. This study found that, compared with the non-POD group, the POD group exhibited higher preoperative levels of IL-6, TNF-α, and MPO. Furthermore, the multivariate analysis showed that IL-6 and TNF-α were the influencing factors of POD in patients with TBI.

IL-6 is an important cytokine that promotes the production of C-reactive protein and fibrinogen, playing a key role in inflammatory responses. It is produced in response to infection or inflammation, leading to a rapid elevation in IL-6 Levels in a short time, peaking within 2 hour. This increase is consistent with the severity of inflammation[26,27]. Monocyte macrophages produce TNF-α, which is expressed only in small amounts in the brain tissue of healthy individuals. While moderate expression of TNF-α has a defensive effect, excessive expression may cause neurotoxicity. Studies have shown that TNF-α levels increase significantly during trauma and inflammatory response, followed by swelling and even necrosis of nerve cells in patients[28,29]. MPO is a functional activation marker of neutrophils and plays a role in the production and regulation of inflammatory responses in the body. Neutrophil infiltration is one of the main factors in the inflammatory response in patients with craniocerebral injuries. In states of inflammation and oxidative stress, MPO catalyzes reactions that generate excessive oxidants to protect the body. However, when the body's antioxidant defense range is exceeded, oxidative stress and tissue damage occurs, aggravating disease progression[30]. IL-6 and TNF-α, much like MPO, exhibit the capacity to promote the secretion of trophic factors by human glial cells to a certain extent, thereby promoting the repair of nerve tissue. However, overactivation of these factors induces chemokine release, triggering local inflammatory cascade burst reactions[31]. Therefore, monitoring these inflammatory factors can effectively evaluate the degree of the inflammatory response in patients.

Studies have found that compared with patients without depression, those with depression are nearly 1.3-9 times more likely to develop delirium, and a history of depression and the presence of subclinical depression levels are both high-risk factors for POD[32]. This study also found that the HAMA and HAMD scores and the proportion of patients with anxiety and depression in the POD group were higher than those in the Non-POD group, which is consistent with the results of the previously mentioned studies[32]. Multivariate analysis demonstrated that HAMA and HAMD scores were risk factors for POD in patients with TBI. Previous studies have also identified a correlation between depression and POD. On the one hand, depression has a certain predictive effect on POD. Depressed patients often show symptoms such as low mood, loss of interest, and sleep disorders, which may further affect their mental state and cognitive function, and increase the risk of POD. On the other hand, some epidemiological studies have included delirium as a risk factor for postoperative depression[33,34]. Thus, both may have similar pathophysiological mechanisms. Functional imbalances of dopaminergic and cholinergic neurotransmitters involved in delirium, abnormal stress, and the inflammatory response of

the hypothalamic-pituitary-adrenocortical axis are also considered to be related to depression[35]. Recent studies have suggested that anxiety and delirium are associated with inflammatory cytokines. Therefore, anxiety is proposed as a new predictor of POD[36]. After migration, peripheral inflammatory cytokines interact with microglia, causing an inflammatory response and the onset of delirium. However, excessive anxiety can lead to tachycardia, hypertension, and arrhythmia, which in turn induce inflammatory responses. In addition, it has been reported that preoperative anxiety can lead to short- and long-term adverse consequences after surgery, such as complications, psychological distress, increased need for analgesics and anesthetics, and decreased quality of life and cognitive ability, which are not conducive to patient recovery[37]. Therefore, preoperative intervention and treatment of patients with emotional disorders can help to improve their psychological state, reduce the strees response to the surgery and the incidence of POD, and improve their experience during the surgical procedure and postoperative recovery. Previous studies have shown that preoperative treatment of emotional disorders can improve the psychological resilience of the patients and reduce their stress response, allowing them to cope better with the stress and challenges that having surgery entail, and improving their prognosis[38].

CONCLUSION

This study analyzed the risk factors related to POD in patients with TBI. We explored the correlation between preoperative inflammatory factors, emotional disorders, and POD in patients with TBI with the aim of reducing the risk of POD. The results showed that GCS score at admission, IVH, IL-6, TNF-α, HAMA, and HAMD were risk factors for POD in patients with TBI. Clinicians can observe the occurrence of these indicators and implement early interventions for high-risk patients, thereby improving their prognosis.

FOOTNOTES

Author contributions: Cao P wrote the manuscript; Jia ZY and Zheng T analyzed the data; Mei T was responsible for revising the manuscript for important intellectual content; all authors read and approved the final version.

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Informed consent statement: All study participants or their legal guardians provided written informed consent for personal and medical data collection before study enrollment.

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ORIGINAL ARTICLE

Retrospective Study

Investigation of the quality of life, mental status in patients with gynecological cancer and its influencing factors

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Abstract

BACKGROUND

Having a gynecological tumor or undergoing treatment can be a traumatic experience for women, as it affects their self-image and sexual relationships and can lead to psychological reactions. Psychological adjustment following cancer occurrence remains a key issue among the survivors.

AIM

To examine the current status of quality of life (QoL), anxiety, and depression in patients with gynecological cancer and to analyze the factors associated with it.

METHODS

Data for 160 patients with gynecological malignancies treated at Shanxi Bethune Hospital from June 2020 to June 2023 were collected and analyzed retrospectively. Patients' QoL was assessed using the European Organization for Research on Treatment of Cancer Quality of Life Questionnaire Core 30 and the Functional Assessment of Cancer Therapy-General Questionnaire. Their emotional status was evaluated using the Self-Rating Anxiety/Depression Scale. The associated factors of anxiety and depression were analyzed.

RESULTS

The overall QoL score of the patients 6 months after surgery was 76.39 ± 3.63 points. This included low levels of social and emotional function and severe fatigue and pain. The scores for physiological, functional, emotional, social, and family well-being exhibited an upward trend following surgery compared with those before surgery. One month after surgery, some patients experienced anxiety and depression, with an incidence of 18.75% and 18.13%, respectively. Logistic analysis revealed that good sleep was a protective factor against anxiety and

depression in patients with gynecological tumors, whereas physical pain was a risk factor.

CONCLUSION
Patients with gynecological malignancies often experience anxiety and depression. By analyzing the factors that affect patients' QoL, effective nursing measures can be administered.

Key Words: Gynecological; Tumors; Quality of life; Anxiety; Depression

Core Tip: Patients diagnosed with cancer experience various emotions. Up to now, numerous papers exploring the association and risk factors between various types of cancer and depressive/anxiety episodes have been published. However, the results of these studies remain inconsistent. The aim of this study was to evaluate the relationship between depression and anxiety mood in gynecological cancer and its risk factors.

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INTRODUCTION

Gynecological malignancies are crucial as they affect the lives and health of women, accounting for 14.4% of new cancer cases among women worldwide[1]. The common types are cervical, ovarian, endometrial, and vaginal cancers[2-5], each of which has a specific symptom burden on the survivor's quality of life (QoL). Over the past few decades, the average life expectancy of patients with gynecologic cancers has increased with the continued development and adoption of interdisciplinary and interprofessional care in clinical practice[6]. Because of the specific location of gynecologic malignancies, surgery usually involves pelvic organ dissection, which results in greater mental stress and psychological pain in these patients compared with patients with other cancer types. This is in addition to the harm and adverse effects caused by surgery and chemoradiotherapy common to all cancer patients[7,8]. Treatment also affects the self-efficacy, QoL, and physical function of cancer patients[9]. Even after treatment, cancer survivors face various difficulties and challenges that affect their QoL, a term that describes the alteration and enhancement of life attributes.

Symptoms such as anxiety, depression, and fatigue are common in all cancer patients[10]. In addition to physical symptoms, patients often struggle with psychological problems[11]. In addition, cancer patients often lack confidence or the ability to effectively manage life after receiving cancer treatment; thus, more information is needed. These cancer-related sequelae may significantly compromise mental health and QoL. Anxiety and depression are a direct threat to the physical and mental health of patients, are very common in clinical practice, and are a major cause of death[12]. Depression and anxiety are more common in patients with cancer than in people without chronic medical conditions; however, the prevalence varies widely[13]. Among patients with cancer, the estimated prevalence of depression is 11%-57%, whereas that of anxiety is 6.5%-23%[14]. Therefore, examining the anxiety and depression status of patients with gynecological cancer and analyzing the influencing factors will be useful for targeted intervention in patients who experience anxiety and depression in clinical practice, avoiding or reducing further physical and mental health damage caused by anxiety or depression, improving patients' QoL, and prolonging their lives.

MATERIALS AND METHODS

Study population

Patients with gynecological malignancies admitted to Shanxi Bethune Hospital between June 2020 and June 2023 were enrolled as the research subjects for this retrospective analysis. The inclusion criteria were as follows: (1) Definite diagnosis of a gynecological malignancy; (2) Age > 18 years; (3) Expected survival > 6 months; (4) Karnofsky Performance Status score ≥ 60; (5) Certain cognitive level with no language communication barriers; and (6) Complete clinical data. The exclusion criteria were as follows: (1) Cancer concomitant with other major diseases; (2) Recent major traumatic or life events; (3) Serious mental disorders; and (4) Incomplete clinical data. Of the 171 questionnaires distributed, 160 valid ones were recovered, with a questionnaire recovery rate of 93.6%.

Data collection

The survey was conducted in the gynecology ward by uniformly trained investigators in the form of face-to-face interviews.

General information questionnaire: The questionnaire was designed by the researcher and patient clinical data were collected, including age, tumor type, ethnicity, education level, annual household income, marital status, number of children born, and working status.

QoL: This survey was conducted on week 1 as well as 1-, 3-, and 6-months after surgery. The European Organization for Research and Treatment on Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the Functional Assessment of Cancer Therapy-General Questionnaire (FACT-G) were used to assess QoL. The QLQ-C30 consists of 30 items covering five functional dimensions (physical, role, emotional, cognitive, and social functioning), three symptom dimensions (fatigue, nausea and vomiting, and pain), one global health status, and six single-item measures (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems). Except for global health status, which was measured on a 7-point Likert scale, the items were graded on a 4-point Likert scale. The final score was linearly transformed, with a total score of 0-100 for each category. The higher the score in the functional and global health status dimensions, the better the QoL. Scores for symptom dimensions and single-item measures are inversely associated with QoL. The FACT-G scale is usually used to measure the QoL of ordinary cancer patients, with a total of 27 items from the following four dimensions: Physical (7 items), social/family (7 items), emotional (6 items), and functional well-being (7 items). Each item is graded on a scale of 0-4, with 0 being not at all, 1 being a little bit, 2 being somewhat, 3 being quite a bit, and 4 being very much. Based on the scoring method of the scale, the four dimensions and the total score are calculated and the total score range is 0-108 points. A higher score suggests better QoL for the research subject.

Depression and anxiety: Depression and anxiety in the patients were assessed on week 1 and 6-months after surgery using the self-rating depression scale (SDS) and self-rating anxiety scale (SAS), respectively. Based on the results using Chinese norms, an SDS score of > 53 is considered depression and an SAS score > 50 indicates anxiety, with higher scores of both representing a higher level of anxiety or depression.

Statistical analyses

SPSS 25.0 was used to analyze the data. Continuous variables (mean ± SD) were comparatively analyzed between groups using a t-test and among groups using one-way analysis of variance. The counting data were expressed as percentages, and the χ^2 test was used. Based on univariate analysis, multivariate logistic regression was used to analyze the influencing factors of anxiety and depression. Tests were two-tailed with $P < 0.05$ indicating statistical significance.

RESULTS

EORTC QLQ-C30 scores of gynecological tumor patients

Compared with the indicators before surgery, the scores of physical, role, emotional, cognitive, and social functioning of postsurgical patients with gynecological cancer exhibited an overall increasing trend (mean global health status: 76.39 ± 3.63 points), of which the level of social and emotional functioning was low. For symptom dimensions, pain had the highest score (26.25 ± 6.46 points), followed by insomnia (21.83 ± 4.95 points) and fatigue (21.44 ± 2.73 points). Meanwhile, the score for financial problems was also high (Table 1).

FACT-G scores of patients with gynecologic tumors

In the FACT-G scoring, the physical, functional, emotional, social, and family well-being scores all exhibited a significant upward trend in patients at 1 week, as well as 1-, 3-, and 6-month after surgery compared with before surgery ($P < 0.05$; Table 2).

SAS and SDS scores

The SDS score for gynecological cancer patients was 41.31 ± 9.88 one week after surgery and 42.28 ± 11.53 one month after surgery, with no statistical significance ($P > 0.05$). In contrast, a significant difference was observed in SAS scores at 1 week (37.98 ± 8.92) and 1 month (43.07 ± 8.58) after surgery ($P < 0.05$; Figure 1).

Univariate analysis of the influencing factors of anxiety and depression

Among the 160 gynecological cancer patients, 30 (18.75%) had anxiety, 29 (18.13%) had depression, and 17 (10.63%) had both anxiety and depression. Univariate analysis of the influencing factors of anxiety and depression revealed that annual household income, working status, body pain, and sleep duration had a significant impact on anxiety (Table 3), whereas annual household income, body pain, and sleep duration significantly influenced depression (Table 4).

Logistic regression analysis of influencing factors of anxiety and depression in patients with gynecological cancer

Multivariate regression analysis revealed that body pain was a risk factor for anxiety and depression, whereas sleep duration ≥ 6 h was a protective factor (Table 5).

DISCUSSION

In general hospitals in China, physical illness often coexists with anxiety and depression[15]. Although anxiety and depression may be early symptoms of physical diseases, they are associated with physical diseases and have various effects on the diseases themselves. The incidence of anxiety was 32.0%-40.0% and that of depression was 25.8%-58.0% in

Table 1 European Organization for Research and Treatment on Cancer Quality of Life Questionnaire Core 30 scores of patients

n = 160	1 week after surgery	1 month after surgery	3 months after surgery	6 months after surgery	*F*	*P* value
Physical functioning	80.31 ± 4.28	84.14 ± 4.52	87.04 ± 4.05	89.96 ± 5.16	133.0	< 0.0001
Role functioning	81.77 ± 5.20	83.73 ± 4.61	86.72 ± 6.34	89.84 ± 4.50	73.25	< 0.0001
Emotional functioning	65.59 ± 4.01	68.17 ± 4.27	70.61 ± 7.34	73.99 ± 7.14	58.90	< 0.0001
Cognitive functioning	83.87 ± 6.09	86.53 ± 5.06	87.91 ± 4.68	88.74 ± 5.09	26.39	< 0.0001
Social functioning	64.09 ± 3.77	66.20 ± 5.74	69.39 ± 2.16	70.38 ± 3.60	82.90	< 0.0001
Global health status	65.49 ± 5.75	69.01 ± 4.70	72.33 ± 3.37	76.39 ± 3.63	174.0	< 0.0001
Fatigue	18.71 ± 1.17	19.58 ± 1.46	20.61 ± 2.33	21.44 ± 2.73	55.82	< 0.0001
Nausea and vomiting	10.17 ± 1.94	10.13 ± 1.83	8.94 ± 1.68	7.44 ± 1.27	91.87	< 0.0001
Pain	23.36 ± 3.55	24.38 ± 5.01	25.30 ± 3.05	26.25 ± 6.46	11.02	< 0.0001
Dyspnea	8.28 ± 1.03	7.97 ± 1.14	7.46 ± 0.93	6.82 ± 1.09	59.47	< 0.0001
Insomnia	19.89 ± 3.82	21.40 ± 4.43	21.81 ± 4.17	21.83 ± 4.95	7.033	0.0001
Appetite loss	6.33 ± 1.17	6.18 ± 1.12	5.44 ± 0.81	5.64 ± 1.04	26.43	< 0.0001
Constipation	4.50 ± 0.56	4.78 ± 0.47	4.25 ± 0.58	4.16 ± 0.84	31.88	< 0.0001
Diarrhea	3.76 ± 0.62	3.71 ± 0.77	3.54 ± 0.73	3.47 ± 0.58	6.585	0.0002
Financial problems	50.65 ± 5.60	52.54 ± 4.52	54.63 ± 5.47	54.98 ± 5.01	24.26	< 0.0001

Table 2 Functional Assessment of Cancer Therapy-General Questionnaire scores of patients

	1 week after surgery	1 month after surgery	3 months after surgery	6 months after surgery	*F*	*P* value
Physical well-being	20.19 ± 1.30	21.61 ± 1.47	23.69 ± 1.57	24.84 ± 1.26	351.0	< 0.0001
Social and family well-being	13.73 ± 1.40	18.17 ± 1.19	19.46 ± 1.23	20.17 ± 1.29	124.3	< 0.0001
Emotional well-being	18.24 ± 1.36	19.34 ± 1.11	20.24 ± 1.31	21.28 ± 1.38	159.1	< 0.0001
Functional well-being	14.58 ± 1.08	14.81 ± 1.07	16.13 ± 1.25	18.66 ± 1.38	387.7	< 0.0001
FACT-G total score	70.74 ± 2.43	73.93 ± 2.24	79.52 ± 2.86	84.94 ± 2.78	934.5	< 0.0001

FACT-G: Functional Assessment of Cancer Therapy-General Questionnaire.

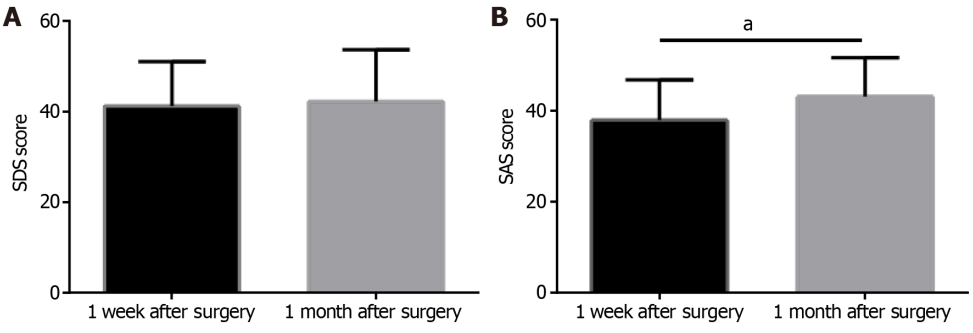

Figure 1 Self-rating anxiety scale and self-rating depression scale of patients. A: Self-rating depression scale scores of patients 1 week and 1 month after surgery; B: Self-rating anxiety scale scores of patients 1 week and 1 month after surgery.[a]*P* < 0.0001. SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

Chinese patients with malignancies. A survey of 3497 adults with anxiety and depression in China revealed statistically higher rates of comorbid anxiety and depression among cancer patients than among adults without cancer (49.69% *vs* 18.37%; 54.90% *vs* 17.50%)[16]. This suggests a high incidence of anxiety and depression among patients with malignancies in China. To effectively treat malignancies and enhance the QoL in patients with cancer, considerable attention should be paid to the prevention and treatment of anxiety and depression.

Table 3 Univariate analysis of influencing factors of anxiety

	Anxiety (*n* = 30)	Non-anxiety (*n* = 130)	χ^2	*P* value
Age (years)			0.401	0.527
< 45	14	69		
≥ 45	16	61		
Tumor type			0.489	0.783
Carcinoma of the cervix	10	48		
Carcinoma of the vulva	5	26		
Endometrial carcinoma	15	56		
Ethnicity			0.036	0.849
Han	20	89		
Ethnic minorities	10	41		
Education level			0.312	0.577
High school and below	17	87		
Bachelor's degree or above	13	43		
Residence			0.041	0.839
Rural	16	72		
Urban	14	58		
Payment mode for medical expenses			0.173	0.677
Medical insurance payouts	22	100		
Out-of-pocket payment	8	30		
Annual household income (ten thousand CNY)			9.842	0.002
< 5	20	46		
≥ 5	10	84		
Marital status			0.390	0.532
Married	19	90		
Unmarried, divorced, or widowed	11	40		
Number of children born			2.342	0.310
None	5	39		
1	16	62		
≥ 2	9	29		
Working status			6.333	0.012
Employed	14	92		
Unemployed or resigned	16	38		
Body pain			16.381	< 0.0001
With	22	43		
Without	8	87		
Daily sleep duration (hour)			15.511	< 0.0001
< 6	20	37		
≥ 6	10	93		

Table 4 Univariate analysis of influencing factors of depression

	Depression (*n* = 29)	Non-depressive (*n* = 131)	χ^2	*P* value
Age (years)			1.563	0.211
< 45	12	71		
≥ 45	17	60		
Tumor type			0.064	0.969
Carcinoma of the cervix	10	48		
Carcinoma of the vulva	6	25		
Endometrial carcinoma	13	58		
Ethnicity			0.111	0.739
Han	19	90		
Ethnic minorities	10	41		
Education level			5.985	0.014
High school and below	8	69		
Bachelor's degree or above	21	62		
Residence			0.188	0.665
Rural	17	71		
Urban	12	60		
Payment mode for medical expenses			0.183	0.669
Medical insurance payouts	23	99		
Out-of-pocket payment	6	32		
Annual household income (ten thousand CNY)			4.410	0.036
< 5	17	49		
≥ 5	12	82		
Marital status			0.300	0.584
Married	21	88		
Single, divorced, or widowed	8	43		
Number of children born			0.204	0.903
None	8	36		
1	15	63		
≥ 2	6	32		
Working status			0.063	0.801
Employed	19	89		
Unemployed or resigned	10	42		
Body pain			30.511	< 0.0001
Yes	25	40		
No	4	91		
Daily sleep duration (hour)			25.011	< 0.0001
< 6	22	35		
≥ 6	7	96		

Table 5 Logistic regression analysis of influencing factors of anxiety and depression

Variables	β	SE	Wald	*P* value	HR	95%CI
Anxiety						
Annual household income ≥ 50000 CNY	-0.792	0.481	2.710	0.100	0.453	0.176-1.163
Employed	-0.853	0.500	2.915	0.088	0.426	0.160-1.134
Presence of body pain	1.551	0.486	10.172	0.001	4.716	1.818-12.232
Sleep duration ≥ 6 hours	-1.581	0.496	10.147	0.001	0.206	0.078-0.544
Depression						
Educational level: Bachelor's degree or above	0.461	0.563	0.671	0.413	1.586	0.526-4.784
Presence of body pain	2.861	0.626	20.455	0.000	16.964	4.974-57.857
Sleep duration ≥ 6 hours	-2.278	0.572	15.861	0.000	0.103	0.033-0.315

β: Intercept; SE: Standard error; Wald: Chi-square value; HR: Hazard ratio; 95%CI: 95% confidence interval.

Anxiety, depression, and concurrent anxiety and depression were documented in 30 (18.75%), 29 (18.13%), and 17 (10.63%) of the 160 patients with gynecological cancer in this study, respectively. Six months after surgery, the global health status of these patients was 76.39 ± 3.63, in which the levels of social and emotional functioning were low and the symptoms of fatigue and pain were serious. In terms of the FACT-G scale, the scores of related parameters, such as physical, functional, emotional, social, and family well-being, exhibited an upward trend; however, the average mental health level of patients was relatively low after 1 month of surgery, which may be because of the transition from the ignorance period (incomplete understanding of the condition) to depression period (fully aware of the severity of the condition and developing obvious negative emotions) or the transition from the acceptance period (psychologically forced to accept) to loss period (falling into a pessimistic and desperate state). With continued treatment and time, physical functioning significantly improved at 3 months following surgery, and patients entered the recognition or acceptance period. After 6 months, the patients gradually entered the adaptation period, during which their mental health significantly improved.

In addition, we found that good sleep status was a protective factor for anxiety and depression in patients with gynecological cancer, whereas body pain was a risk factor. Sleep disturbance is a common and significant complaint in patients with cancer, with up to 95% complaining of sleep disturbance/disability during diagnosis, treatment, and even after surviving 10 years[17]. Savard *et al*[18] conducted a study on cancer survivors and found that 52% had difficulty sleeping, with 58% reporting cancer-induced or exacerbated sleep problems. In a study by Hajj *et al*[19], higher levels of anxiety and depression were observed in patients with breast cancer with cognitive impairment and poor sleep quality/insomnia. Therefore, good sleep quality and duration are protective factors against anxiety and depression in patients with gynecological cancer. Cancer pain is a multidimensional factor that goes far beyond a nociceptive biochemical signal, with up to half of all cancer patients regularly experiencing pain. Because of its complex etiology, pain manifests as nociceptive, neuropathic, nociceptive, and psychogenic[20,21]. Pain has a significant impact on overall QoL by affecting physical, psychological, and spiritual aspects[22]. In a study of the Austrian population by Unseld *et al*[23], increased pain levels were strongly associated with psychiatric symptoms in patients with cancer.

This study have several limitations. First, this was a retrospective study, which did not allow the randomization of patients in either group. Thus, the similarity of patients in groups is jeopardized and potentially results in selection bias. Moreover, this study had a small sample size from a single-center study, which may have resulted in differences between both groups. Second, the treatment variability should have been mentioned. This study did not account for variations in treatment modalities, such as surgery type, chemotherapy regimens, or radiation therapy. These treatments can differ in their efficacy, side effects, and impact on QoL, anxiety, and depression. Third, the follow-up time was too short to determine long-term outcomes. A longer follow-up period would provide a more comprehensive understanding of the observed changes in outcomes over time. Fourth, the study solely focused on quantitative measures, such as questionnaires. The absence of qualitative data, such as patient interviews or open-ended questions, limits the opportunity to gain further insight into the patient's experiences and perspectives regarding QoL, anxiety, and depression. Therefore, well-designed, randomized, and controlled trials with prospective data collection, long-term follow-up, and sample size calculation are required to confirm our findings.

CONCLUSION

In summary, patients with gynecological malignancies often experience anxiety and depression. By analyzing the factors that affect their QoL, effective nursing measures may be provided to improve QoL. Mental health treatment options for such women should be strengthened to reduce the burden of increased mental symptoms.

FOOTNOTES

Author contributions: Shang HX and Wu SH conceived and designed research; Shang HX, Ning WT, Sun JF, Guo N, Guo X, Zhang JN and Yu HX collected data and conducted research; Shang HX analyzed and interpreted data; Shang HX and Wu SH wrote the initial draft; Shang HX revised the manuscript; all authors read and approved the final version of the manuscript.

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ORIGINAL ARTICLE

Observational Study

Clinical study of chemotherapy-related cognitive impairment in patients with non-Hodgkin lymphoma

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Abstract

BACKGROUND

Chemotherapy for malignant tumors can cause brain changes and cognitive impairment, leading to chemotherapy-induced cognitive impairment (CICI). Current research on CICI has focused on breast cancer and Hodgkin's lymphoma. Whether patients with non-Hodgkin's lymphoma (NHL) undergoing chemotherapy have cognitive impairment has not been fully investigated.

AIM

To investigate whether NHL patients undergoing chemotherapy had cognitive impairments.

METHODS

The study included 100 NHL patients who were required to complete a comprehensive psychological scale including the Brief Psychiatric Examination Scale (MMSE) at two time points: before chemotherapy and within 2 wk of two chemotherapy courses. A language proficiency test (VFT), Symbol Number Pattern Test (SDMT), Clock Drawing Test (CDT), Abbreviated Daily Cognition Scale (ECog-12), Prospective and Retrospective Memory Questionnaire, and Karnofsky Performance Status were used to assess cognitive changes before and after chemotherapy.

RESULTS

The VFT scores for before treatment (BT) and after treatment (AT) groups were 45.20 ± 15.62, and 42.30 ± 17.53, respectively (t -2.16, $P < 0.05$). The CDT scores were 8 (3.5-9.25) for BT and 7 (2.5-9) for AT groups (Z -2.1, $P < 0.05$). Retrospective memory scores were 13.5 (9-17) for BT and 15 (13-18) for AT (Z -3.7, $P < 0.01$). The prospective memory scores were 12.63 ± 3.61 for BT and 14.43 ± 4.32 for AT groups (t -4.97, $P < 0.01$). The ECog-12 scores were 1.71 (1.25-2.08) for BT and 1.79

(1.42-2.08) for AT groups (Z -2.84, $P < 0.01$). The SDMT and MMSE values did not show a significant difference between BT and AT groups.

CONCLUSION

Compared to the AT group, the BT group showed impaired language, memory, and subjective cognition, but objective cognition and execution were not significantly affected.

Key Words: Non-Hodgkin's lymphoma; Hodgkin lymphoma; Lymphoma cognitive impairment; Chemotherapy-related cognitive impairment; Clinical study

Core Tip: The cognitive status of patients with non-Hodgkin's lymphoma before and after chemotherapy was assessed using various cognitive scales. We observed chemotherapy-related cognitive impairment. Patients with non-Hodgkin's lymphoma undergoing chemotherapy may experience chemotherapy-related cognitive impairment. The main manifestations were language, memory, and visuospatial dysfunction. Frontal lobe injury was more obvious, but no clear difference was observed in executive function.

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INTRODUCTION

Lymphoma is a solid tumor that originates from the immune system and can occur at any age and in any part of the body. Its clinical manifestations vary; however, the typical presentation includes painless and gradually enlarging lymph nodes. It can also invade extranodal organs such as the nasopharynx, gastrointestinal tract, bone, and skin, leading to organ damage[1].

Lymphomas are divided into two major categories: Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). NHL is produced by T cells, B cells, NK cells, or histiocytes after antigen stimulation, and the tumor can also spread to the whole body, thus affecting organs throughout the body. NHL accounts for about 90% of all lymphomas and is one of the most common malignant tumors of the lymphopoietic system[2,3].

According to the 2015 global cancer statistics, there were over 380000 new cases of NHL worldwide in 2012 with the highest incidence in developed countries but a lower mortality rate compared to that in developing countries[4]. NHL ranked 8th among new malignant tumors in men and 10th among women, with over 180000 new cases in developed countries, and 7th among men and 10th among women, with over 200000 new cases in developing countries. Regarding deaths, NHL accounts for over 110000 male deaths worldwide, placing it 10th among global causes of male cancer-related deaths, and 9th among developing countries. However, it does not rank in the top 10 causes of male tumor-related deaths in the world or developed countries[5].

The rapid development of comprehensive cancer treatments has significantly improved the overall survival rate of cancer patients. With continuous improvements in treatment and economic levels, after standardized comprehensive treatment, the 5-year survival rate of most NHL patients can exceed 70%[6-8].

Previous studies have shown that chemotherapy for malignant tumors can cause brain changes and cognitive impairment, leading to chemotherapy-induced cognitive impairment (CICI). At present, CICI is often defined as a group of cognitive impairments occurring in tumor survivors during or after chemotherapy, including the ability to pay attention, memory, concentration, learning, understanding, language, judgment, reasoning, logical thinking, behavior, and execution[9,10].

Up to 75% of patients experience cognitive impairment during treatment and 35% experience cognitive impairment several years after treatment completion, which reduces the patient's quality of life[11,12].

Individuals with CICI often describe their cognitive problems as impaired memory and verbal fluency, slowed thought processes, and a shortened attention span. In some patients with breast cancer, cognitive impairment after chemotherapy manifests in speech and visuospatial abilities[13].

If left unmanaged, CICI can impair the performance of the individual at work and home and ultimately reduce the quality of life. CICI can also lead to long-term cognitive impairment. Some studies suggest that older patients with CICI have a 10%–15% chance of developing dementia per year, whereas patients without CICI have a probability of approximately 1%–2.5% per year[14-16]. Current research on CICI focuses on breast cancer and Hodgkin's lymphoma[17,18]. Lymphoma is a solid tumor that can occur at any age and in any part of the body, and NHL accounts for about 90% of all lymphomas. Therefore, this study investigated whether NHL patients undergoing chemotherapy had cognitive impairment.

MATERIALS AND METHODS

This prospective study was approved by the ethics committee of Suzhou Kowloon Hospital, Shanghai Jiao Tong University School of Medicine. Signed informed consent was obtained from all patients before inclusion in the study.

Patient recruitment and selection criteria

The patients were enrolled in the study based on specific inclusion and exclusion criteria. The inclusion criteria were as follows: (1) Pathological diagnosis of NHL; (2) Age 20 to 60 years; (3) Ability to provide informed consent; (4) No language barriers; and (5) Patients received standard chemotherapy regimens according to the NCCN guidelines. Exclusion criteria: (1) Current or previous diagnosis of brain tumor (primary or secondary); (2) Hydrocephalus, any type of dementia; (3) Mental disorders and other diseases that may affect cognitive function; (4) Life expectancy of less than 6 mo; (5) Current or past history of alcohol abuse; (6) Current or previous history of head trauma and brain surgery; (7) Hormone therapy (estrogen and progesterone compounds); (8) Active infection; (9) Thyroid disease; and (10) Underwent stem cell transplantation.

Study design

Participants were evaluated at two time points: Before treatment (BT) and 2 wk after two courses of chemotherapy [after treatment (AT)]. The evaluation included a complete comprehensive psychological assessment which comprised the Brief Psychiatric Examination Scale (MMSE), Verbal Fluency Test (VFT), Symbolic Number Pattern Test (SDMT), Clock Drawing Test (CDT), Simplified Daily Cognitive Scale (ECog-12) and Prospective and Retrospective Memory Questionnaire and Karnofsky Performance Status score.

Statistical analysis

Data analysis was performed using SPSS version 24.0, employing a two-tailed significance level of 0.05. A descriptive analysis was carried out for each item. The cytokine and psychological levels were analyzed before and after treatment. Mean ± standard deviation (SD) was used to describe normally distributed data, while non-normal distributed data were described by M (P25 and P75). A paired *t*-test was used for comparison.

RESULTS

A total of 100 NHL patients were included in this study. The demographic characteristics and clinical information of the participants are shown in Table 1. The median age of NHL patients in this study was 47 years, and the majority were between 43 years and 55 years. Of the participants, 49 were males (49%) and 51 females (51%). The median years of schooling was 7.5, predominantly ranging between 6 years and 8 years. According to the Ann Arbor staging system, 62 patients (62%) had stage II NHL, 26 (26%) had stage III, and 12 (12%) had stage IV NHL.

The main results are shown in Table 2. The MMSE scores of the BT and AT groups were 27 (23.75–29), and 27 (23.25–29), respectively. After conducting the Wilcoxon rank-sum test on the relevant samples, the statistical value Z was -1.16 and P was 0.247, indicating that the difference was not statistically significant. The VFT scores of the BT group were 45.20 ± 15.62, and that of the AT group was 42.30 ± 17.53. Using a paired-sample *t*-test, the statistical *t*-value was 2.16, (P < 0.05), indicating a statistically significant difference. The SDMT scores were 24.5 (10.5–36) in the BT and 22.5 (12–33) in the AT groups. The Z was 0.69, (P -0.492), indicating that the differences were not statistically significant. The value of CDT in the BT group was 8 (3.5–9.25), and that in the AT group was 7 (2.5–9). The Z value was -2.1 (P < 0.05), suggesting a statistically significant difference. The retrospective memory (RM) values of the BT and AT groups were 13.5 (9–17) and 15 (13–18), respectively. The Z value was -3.7 (P < 0.01), and the difference was statistically significant. The prospective memory (PM) values of the BT and AT groups were 12.63 ± 3.61, and 14.43 ± 4.32 respectively. The *t*-value was -4.97 (P < 0.01), and the difference was statistically significant. The value of ECog-12 in the BT group was 1.71 (1.25–2.08), and that in the AT group was 1.79 (1.42–2.08). The Z was -2.84 (P < 0.01), and the difference was statistically significant.

DISCUSSION

Currently, there are many studies on cognitive impairment after chemotherapy, mostly focusing on breast and prostate cancers, whereas there are relatively few studies on NHL[19-21]. With the continuous improvement in NHL treatment, the survival period of patients is relatively long, emphasizing the need to address the quality of life of these patients. Therefore, it is imperative to study CICI in NHL patients.

It has been documented that lymphoma patients may have lower cognitive performance after chemotherapy, exhibiting poor performance in executive function and attention. Some patients also report severe fatigue and a significant decline in quality of life. Patients with chronic lymphocytic leukemia undergoing 3 mo of chemotherapy may experience impairment in executive function and memory[22]. In mouse experiments, chemotherapeutic drugs have been shown to impair memory for up to 12 h, passive avoidance learning, and new object recognition. Additionally, the cognitive performance of patients with breast cancer significantly differs at 1, 3, and 6 mo after chemotherapy compared to before chemotherapy, with a gradual decline in their cognitive ability[23]. Chemotherapy can also affect memory and damage processing speed, attention, and executive functions.

Table 1 Basic information for patients with non-Hodgkin's lymphoma

Clinical characteristics	Value
Age in yr	47 (43–55)
Sex	
Male	49
Female	51
Education in yr	7.5 (6–8)
Ann Arbor stage	
II stage	62
III stage	26
IV stage	12

Data are *n* or *n* (range).

Table 2 Comparison of cytokine and psychological tests before and after chemotherapy

Parameter	BT group	AT group	*t*/*Z* value	*P* value
MMSE	27 (23.75–29)	27 (23.75–29)	-1.16	0.24
VFT	45.20 ± 15.62	42.30 ± 17.53	2.16	< 0.05
SDMT	24.5 (10.5–36)	22.5 (12–33)	0.69	0.49
CDT	8 (3.5–9.25)	7 (2.5–9)	-2.1	< 0.05
RM	13.5 (9–17)	15 (13–18)	-3.7	< 0.01
PM	12.63 ± 3.61	14.43 ± 4.32	-4.97	< 0.01
ECog-12	1.71 (1.25-2.08)	1.79 (1.42-2.08)	-2.84	< 0.01

Data are *n* (range) or mean ± standard deviation. AT: After treatment; BT: Before treatment; CDT: Clock Drawing Test; ECog-12: Abbreviated Daily Cognition Scale; PM: Prospective memory; RM: Retrospective memory; SDMT: Symbol Number Pattern Test; VFT: Verbal Fluency Test; MMSE: Brief Psychiatric Examination Scale (Mini-Mental State Examination).

Most of the existing mechanisms revolve around the direct toxic effects of drugs on nerve cells, including the destruction of the blood-brain barrier, loss of neurons in the hippocampus, white matter damage, neuronal inflammatory damage, oxidative stress, *etc*[24,25]. However, the exact underlying mechanisms have not been fully elucidated. Endodermal injury plays a key role in the process of chemotherapy-related cognitive dysfunction. It was first reported that Bortezomib was involved in the inhibition of autophagic lysosome function of cerebral vascular endothelium through TFEB, which elucidates that cerebral vascular endothelium TFEB negatively regulates STAT3 transcription of IL23A. It was further demonstrated that IL23A, as a signaling molecule, is involved in the communication between endothelium and microglia, mediating microglia activation and synaptic phagocytosis[26].

In this study, we found that the VFT and CDT scores of NHL patients significantly decreased in the AT group compared to that of the BT group. Additionally, the scores of RM, PM, and ECog-12 significantly increased in the AT group. However, no significant differences were observed in MMSE and SDMT. The VFT scale is often used to evaluate instantaneous verbal memory, spontaneous verbal motor function, thinking organization, and interference inhibition abilities. The decreased scores in the AT group suggest impaired language function and frontal lobe damage in NHL patients after chemotherapy. The CDT score is often used to assess executive abilities by integrating tasks such as spatial organization, numerical order, and time comprehension. The decline in CDT scores in the AT group indicates impaired visuospatial ability in patients with NHL after chemotherapy mirroring the findings in the VFT score, which indicates frontal lobe dysfunction. The RM and PM scores reflect patient memory function. The increase in scores in the AT group indicates impaired retrospective and prospective memories in NHL patients after chemotherapy. The ECOG-12 scores indicate subjective cognitive changes. An increase in scores in the AT group indicated impaired subjective cognition in NHL patients.

Nevertheless, there was no significant change in the SDMT scores before and after chemotherapy, suggesting that patients did not experience chemotherapy-induced changes in visual processing, sensory functions, visuospatial abilities, or scanning movements. Moreover, there was no significant change in MMSE scores before and after chemotherapy, which could be related to the relatively short follow-up time in this study, leading to the lack of statistical difference in the

MMSE score. Additionally, some studies have pointed out that MMSE may not be highly sensitive in detecting mild cognitive impairment.

CONCLUSION

In summary, compared with the BT group, the AT group showed impairments in language, memory, and subjective cognition, but objective cognition and executive performance were not significantly affected. This may be attributed to the fact that the second test was conducted within 2 wk after the two courses of chemotherapy, which might have resulted in only partial damage to cognitive functions. In this study, impairments were mainly observed in language, memory, and visuospatial abilities, with more noticeable frontal lobe injury, while no clear difference was found in executive function.

FOOTNOTES

Author contributions: Wang QL and Chen ZL designed the study; Wang QL, Chen ZL, Xu HY, Wang Y, Wang YL, and Lin PN performed the research; Wang QL, Chen ZL, Xu HY, Wang Y, Wang YL, and Lin PN contributed new reagents and analytical tools; Wang QL and Chen ZL analyzed the data and wrote the manuscript; All authors have read and approved the final version of the manuscript.

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ORIGINAL ARTICLE

Observational Study

Emotional differences based on comments on doctor-patient disputes with varying levels of severity

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Abstract

BACKGROUND

The risks associated with negative doctor-patient relationships have seriously hindered the healthy development of medical and healthcare and aroused widespread concern in society. The number of public comments on doctor-patient relationship risk events reflects the degree to which the public pays attention to such events.

AIM

To explore public emotional differences, the intensity of comments, and the positions represented at different levels of doctor-patient disputes.

METHODS

Thirty incidents of doctor-patient disputes were collected from Weibo and TikTok, and 3655 related comments were extracted. The number of comment sentiment words was extracted, and the comment sentiment value was calculated. The Kruskal-Wallis *H* test was used to compare differences between each variable group at different levels of incidence. Spearman's correlation analysis was used to examine associations between variables. Regression analysis was used to explore factors influencing scores of comments on incidents.

RESULTS

The study results showed that public comments on media reports of doctor-patient disputes at all levels are mainly dominated by "good" and "disgust" emotional states. There was a significant difference in the comment scores and the number of partial emotion words between comments on varying levels of severity of doctor-patient disputes. The comment score was positively correlated with the number of emotion words related to positive, good, and happy) and negatively

correlated with the number of emotion words related to negative, anger, disgust, fear, and sadness.

CONCLUSION
The number of emotion words related to negative, anger, disgust, fear, and sadness directly influences comment scores, and the severity of the incident level indirectly influences comment scores.

Key Words: Doctor-patient relationship; Doctor-patient dispute; Comments; Emotional differences; Weibo; TikTok

Core Tip: This study applies sentiment analysis methods to specific instances of doctor-patient disputes and explores differences in sentiment among different levels of incidents. Sentiment analysis using a combination of manual and machine methods compensates for the lack of using a single method to some extent. This study selected emotion as an entry point to explore the factors influencing comment scores on doctor-patient dispute incidents.

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INTRODUCTION

There has been steady progress in the extent of medical and health system reforms. Consequently, terms such as "doctor-patient relationship" have become a hot topic of discussion among the public, and phrases such as "medical accidents" and "violent injury to doctors" have appeared in the media, thereby triggering ongoing concern and public discussion.

The Chinese government has always attached great importance to the establishment of harmonious doctor-patient relationships, as evidenced by the implementation of measures such as mediation mechanisms and dispute prevention mechanisms. However, doctor-patient relationships in China have not fundamentally improved, and the number of doctor-patient judicial cases has been increasing annually. With the rapid development and wide application of internet-based self-media technology, platforms such as Weibo and TikTok have become important channels through which the Chinese public can freely express their opinions[1]. Individuals use network platforms as information exchange channels; specifically, they use text, pictures, video, and other diversified text forms to express their views and vent their emotions regarding hotspot reports on doctor-patient disputes, thereby leading to diverse expressions of emotional output. As doctor-patient disputes continue to ferment in relevant social media reports and comments from the public, healthcare incidents that are closely related to people's lives and health have gradually become a hot topic of public opinion online [2]. The emotional impact of public discourse in the online evolution of doctor-patient disputes is increasing, thus generating a variety of significant social impacts and subconsciously guiding and changing the public's emotions and perceptions of both doctors and patients during incidents.

Emotional differences among the public in doctor-patient dispute incidents are an important factor influencing cognitive differences in doctor-patient relationships. Thus, the study of emotional differences in the evaluation of doctor-patient disputes provides new research topics and ideas for new research directions with respect to the rational resolution of doctor-patient disputes as well as proper guidance for the development of healthy doctor-patient relationships. From the perspective of emotional transmission, research on real comments on social media platforms, the public's emotional expression, the nature of the output content, the process of the evolution of emotional dynamics, and the triggers of emotion generation in doctor-patient disputes can help to deepen our understanding of doctor-patient disputes and to establish a reasonable mechanism for mitigating the risk of medical malpractice.

Emotion is a generic term for a range of subjective cognitive experiences. This term describes a person's attitudinal experience of objective things and the corresponding behavioral responses. Emotion is generally considered a psychological activity that is mediated by the individual's wants and needs. Furthermore, it is an internal subjective experience that is always accompanied by some kind of external manifestation that is interpreted as a behavioral trait[3]. Public comments on incidents involving doctor-patient disputes are external manifestations of emotions, as these comments involve making subjective emotional evaluations of the doctor and patient in objective incidents of doctor-patient disputes through perspectives of individuals in the public.

As the outcomes of a doctor-patient dispute progress, the position and emotional state of the public's evaluative discourse change accordingly. Recent research on doctor-patient disputes has focused on factors influencing doctor-patient disputes and countermeasures but has not examined changes in public emotions and positions caused by news reports on doctor-patient disputes. Therefore, we take emotions as the entry point in this study, and explore differences in emotions at different levels of doctor-patient dispute incidents after grading doctor-patient dispute incidents according to their severity. From the perspective of the emotional state of public opinion, we propose rationalized suggestions for establishing a harmonious doctor-patient relationship and publishing truthful and reliable news reports on doctor-patient

disputes.

Current research status: Domestic and foreign scholars have conducted numerous studies of topics related to doctor-patient disputes, online public opinion, and textual sentiment analysis. Recent research on doctor-patient disputes has mainly focused on the analysis of the causes of doctor-patient disputes and countermeasures and has relied on the basic framework of the doctor's image, doctor-patient communication, social media coverage and public opinion control. Domestic and foreign scholars mainly attribute doctor-patient disputes to a lack of in-depth communication between doctors and patients[4], a lack of trust between doctors and patients[5], information asymmetry[6], and an uneven distribution of healthcare resources[7]. However, few researchers have focused on the moderating role of emotions in incidents of doctor-patient dispute. Therefore, in this study, we explored the influence of emotion on doctor-patient dispute incidents, examined the differences in public emotion at different levels of doctor-patient dispute incidents and investigated the influence of the public's emotional intensity and the position they represent in their comments on doctor-patient disputes.

Wei *et al*[8] proposed that in an online virtual environment, both the truthfulness and symmetry of information can lead to cognitive bias in the public. Official media reports of doctor-patient disputes are more authentic and can affect the public's cognitive judgement and emotional attitudes towards the behavior of doctors and patients in these disputes. Social perspectives develop through social interaction[9]. The spread of numerous perspectives is accomplished through interactions between subjects in society[10,11]. The emotions expressed by the public affect the width and breadth of the dissemination of doctor-patient disputes and the emotions generated by doctor-patient disputes and the positive emotional output advocated by the mainstream of society have a mutually interfering and antagonistic effect. Negative emotions can even become the cause of the user's negative behaviors, thereby affecting the development of incidents. The opinions of public figures can also have a direct impact on the development of an incident. The better their arguments are and the more moderate their attitudes are, the more likely they are to steer public opinion[8]. Doctor-patient relationships in online public opinion refer to the sum of all public emotions, attitudes, opinions, and subsequent impacts on hot healthcare incidents that occur on the internet[12]. Doctor-patient relationships in online public opinion systems have the characteristics of general online public opinion, such as negative topics, distorted information, and difficulty in control [13,14]. The wrongdoing of the responsible side in doctor-patient disputes based on news reports can easily affect public emotions and opinions.

With the development of the internet, text sentiment analysis has gradually become a popular research topic in natural language processing. Sentiment detection is closely related to sentiment analysis, which uses natural language processing [15] and involves identifying the positive, negative, and neutral nature of a text. Sentiment analysis involves seven basic emotions, disgust, fear, happiness, anger, guilt, sadness and shame[16,17]. Extracting sentiment information from comment texts requires sentiment analysis techniques, which involves sentiment classification. Currently, sentiment classification is either machine learning-based [18] or lexicon-based[19]. Pang *et al*[18] were early researchers working on machine learning-based sentiment analysis of text. They applied plain Bayesian, maximum entropy, and support-vector machine algorithms to analyze the sentiment of film reviews. Their results showed that the support-vector algorithm performed better than the other approaches. In a deep learning model, Su *et al*[20] used sentence-level analysis to identify the overall sentiment polarity conveyed in a given sentence. Zhang *et al*[21] proposed a method for classifying emotions based on emotion-specific word vectors. They constructed a heterogeneous network to obtain the vectors and then after obtaining them, they trained a long short-term memory network for emotion classification. In their approach, Zhang *et al* [22] extended the sentiment lexicon of the Dalian University of Technology by adding related domain-name lexicons, such as the network lexicon, emoji lexicon, and others. Finally, they computed the sentiment extremes of the Weibo comment information by transforming the uniform weights of its sentiment classification. Zhu *et al*[23] developed and used a method based on semantic rules and weighted expressions to classify the sentiment of Chinese microblog comments. In a detailed empirical study on sentiment classification, Liu *et al*[24] used various multilabel classification methods, including the Dalian University of Technology Sentiment Lexicon, National Taiwan University Sentiment Lexicon, and HowNet lexicon. They concluded that the Dalian University of Technology Sentiment Lexicon was the best among the 2014 different sentiment lexicons. In this study, we used the Dalian University of Technology Sentiment lexicon and applied both manual and machine classification methods to perform text sentiment analysis. The use of both machine and manual analysis minimizes the drawbacks of isolating single emotion words by machine analysis. Sentiment value calculation can be carried out by using a machine to extract emotion words and manual annotation to review and comment.

Many domestic and foreign scholars have conducted studies on the cause of doctor-patient disputes and analyzed textual sentiments, but few have examined the emotional tendencies reflected by public evaluation of reports of doctor-patient disputes. In this study, we aimed to explore the difference of emotions associated with the severity of doctor-patient dispute incidents. We wanted to investigate the impact of the intensity of emotions and the positions represented by public comments about these incidents. Based on the results of existing studies, we propose three hypotheses.

Hypothesis 1: Comment scores for doctor-patient dispute incidents are related to the severity of the incident (*i.e.* the severity of the damage caused by the behavior of the responsible at-fault side). Hypothesis 2: There is a positive correlation between the severity of the incident and the number of words related to sadness (*i.e.* the tendency of the public to feel pity and sadness for the victim) in the public comments. Hypothesis 3: The intensity of negative emotions brought about by the negative-emotion words in public comments has a direct effect on the incident comment score and influence of the opinion. This empirical study used a sentiment classification method based on sentiment lexicon analysis of Weibo and TikTok comments. The intersentence and organizational structure rules are shown in Figure 1.

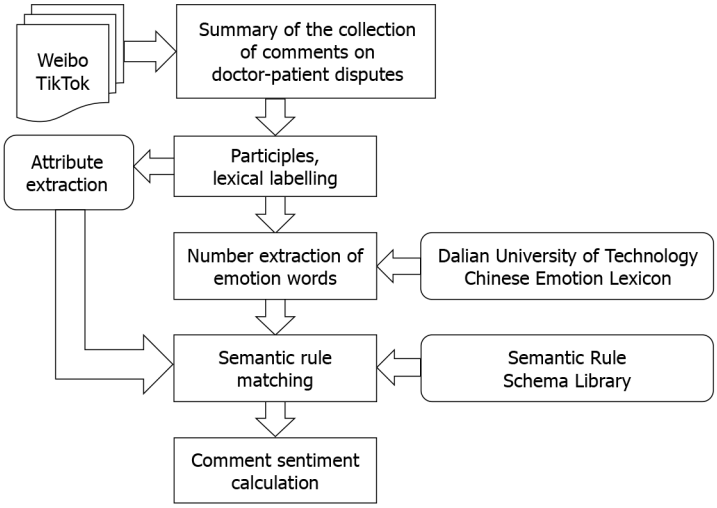

Figure 1 Conceptual model of the sentiment classification method for Weibo and TikTok comments.

MATERIALS AND METHODS

Sample and data collection

We collected and collated 30 doctor-patient dispute incident reports from social media platforms (*e.g.*, Weibo and TikTok). The incidents were manually graded by severity. Level I incidents included verbal conflicts between doctors and patients (*e.g.*, a woman was treated rudely and had an argument with hospital staff after discussing cost issues). Level 2 incidents included physical conflict between doctor and patient (*e.g.*, Shanghai Sixth Hospital notified medical staff of physical conflict). Level 3 incidents included doctor-patient disputes leading to injuries (*e.g.*, in Wuhan, a man with a knife hacked a doctor and was detained). Level 4 incidents included doctor-patient disputes leading to fatalities (*e.g.*, in Hefei, a 27-year-old female patient died in the hospital due to medication). There were 12 level 1, 4 level 2, 9 level 3, and 5 level 4 cases.

Manual text preprocessing

Emoticons, pictures, web links, and the symbol @, which is used to mention someone, frequently appear in the text of Weibo and TikTok comments. These elements not only enrich the text but also pose some difficulties to the study. Consequently, The text was preprocessed for the analysis, and the symbol "@username" was used in Weibo and TikTok comments to tell someone something or to receive someone's attention: (1) Preprocessing had no substantial impact on sentiment analysis, so it was filtered; (2) As the comments collected for the analysis corresponded to the topic, instances of "#Theme#" were ignored and filtered directly; (3) Web links, animations, videos, pictures, and emoticons were filtered; and (4) To avoid loss of comments, traditional Chinese was converted to simplified Chinese and English was converted to Chinese.

We collected and organized comments related to relevant incidents based on graded doctor-patient disputes. We collected a total of 3655 comments after manual text preprocessing. We collected and organized comments related to relevant incidents based on graded doctor-patient disputes. Examples of the collected comments are shown in Table 1.

Construction of a lexicon of relevant emotions

Some of the more mature emotion lexicons studied in China are HowNet, the NTUSD of National Taiwan University, and the Dalian University of Technology Chinese Emotion Vocabulary Ontology Database. In this study, we used the Dalian University of Technology Chinese emotion lexical ontology database as the basic emotion lexicon. Additionally, the negative lexicon was taken into consideration. The Chinese emotion vocabulary ontology database of Dalian University of Technology has 27467 words. The lexical categories in the emotion vocabulary ontology are divided into seven categories: Noun, verb, adjective, adverb, network neologism, idiom, prepositional phrase, and prepositional phrase. The final vocabulary ontology divides emotions into seven categories and twenty-one subcategories: "happy", "good", "angry", "sadness", "fear", "disgust", and "surprise". The sentiment intensity was classified into five classes, with 1 being the lowest and 9 being the highest. Each word corresponds to a polarity under each category of emotion, where 0 represents neutrality, 1 represents positive, 2 represents negative, and 3 represents both positive and negative. The polarity value of 2, representing pejorative, was changed to -1 in this study to facilitate subsequent calculations. Words with both positive and negative properties were manually judged to be positive or negative based on the context of each comment. We modified the polarity and intensity of the comments to better calculate the sentiment value by changing the polarity*intensity to weights. The formula for the emotion word weights of the vocabulary was:

$$s(w) = v(w)p(w)$$

where, s(w) denotes the emotional word weight of the lexicon, v(w) denotes the emotional intensity of the lexicon, and p(w) denotes the emotional polarity of the lexicon. An example of the basic sentiment lexicon is shown in Table 2. In

Table 1 Examples of collected comments on incidents of doctor-patient disputes

Serial number	Comments
1	Doctor-patient conflicts are not without cause
2	Not all people are good, and not all doctors are good
3	There are problems on both sides
4	Do the right thing. If the doctor doesn't do a good job, complain to him
5	I think the doctor's attitude is very bad now
6	Medical ethics are important
7	Where there is a cause, there is an effect. In particular, some patients are already suffering from illnesses, coupled with the irresponsibility of doctors, so it is only right that some doctors have been killed because of doctor-patient disputes
8	Are patients the only ones to blame for doctor-patient conflicts?

Table 2 Examples of basic emotion lexicons

Word	Lexical category	Intensity	Polarity	Weight
Dependency	Verb	1	0	0
Careful	Adjective	3	1	3
Eccentric	Adjective	1	-1	-1
Guffaw	Verb	5	-1	-5

addition, we used a negative lexicon to further improve the accuracy of commenting on sentiment judgements. The negation lexicon included a total of 71 words. Negative words have the opposite meaning of the original sentence, so the weight of the negative words was set to -1. An example of the negation lexicon is shown in Table 3.

Extracting the number of emotion words in text using the Python algorithm

Pandas were used to read the data, and the data were imported into the Dalian University of Technology Chinese emotion vocabulary ontology database using "word", "lexical category", "lexical number", "lexical number", "emotion classification", "intensity", and "polarity". The list of emotion words was collated according to the seven major emotion divisions, and the number of emotion words in each of the collected comments was statistically counted based on the seven emotion divisions of "happy", "good", "angry", "sadness", "fear", "disgust", and "surprise".

Sentiment values are manually calculated for the extracted comment data

The comment data was analyzed using the sentiment lexicon and Python was to extract the number of emotion words. We subsequently calculated the sentiment value for each text comment manually. S(w) denotes the weight of the emotion word, O denotes the sentiment value in a single sentence, and S denotes the sentiment value of all the sentences in a comment combined. An example of a specific situation in a comment is shown below. Because the sentiment value of each comment depends on the weight of the emotion words, we propose that the sentiment value of a single sentence be calculated as:

$$O_1 = S(w_1) + S(w_2) + \cdots + S(w_k)$$

where K is the number of emotion words in the sentence.

When an emotion word followed a negative word, the emotion word was interpreted to express the opposite meaning, and the sentiment value of the comment was related to the number of negative words. The sentiment value changed when the number of negatives was odd, and the polarity of the emotion words was reversed. When the number of negatives was even, the polarity of the emotion words and the sentiment value were in agreement. Therefore, when there were negatives, the equation for the emotion words was:

$$O_2 = (-1)^n * S(w)$$

where n is the number of negatives in the sentence. In summary, if the above possible scenarios were present in a comment, the formula for calculating the comment sentiment value was:

$$S = \sum_{i=1}^{2} O_i$$

Statistical analysis

The Python language was used to extract the number of emotion words in the comments of the collected incidents based on the sentiment lexicon. The sentiment score of the comments was calculated by manually reviewing the number of emotion words in the extracted comments. SPSS 26.0 statistical software (IBM Corp., Armonk, NY, United States) was

Table 3 Negative lexicon examples

Word	Weight	Quantity
Didn't, no, not, couldn't, rarely, never, terminated, missing, never	-1	71

used to explore whether there were differences in the number of words and comment scores for each emotion across the four different levels of incidence using the Kruskal-Wallis *H* test. Correlation analysis was performed to examine the association between incident levels, the number of words in each emotion, and comment scores. Multiple stepwise regression analysis were used to explore the factors influencing the comment scores. Differences were considered to be statistically significant at $P < 0.05$.

RESULTS

Python was used to count the number of emotion words in each comment that was collected. Positive = happy + good + surprise, and negative = anger + sadness + fear + disgust. The results are shown in Table 4. The number of emotion words were extracted from 3655 comments related to 30 doctor-patient disputes. The 1608 comments for level-1 incidents (verbal conflicts) contained a total of 58 emotion words. These words were distributed across seven categories: "anger" (3.6%), "disgust" (68.7%), "fear" (8.0%), "sadness" (9.9%), "surprise" (1.1%), "good" (54.6%), and "happy" (9.6%), with 1104, 128, 159, 17, 878, and 155 words in each category, respectively. The 486 comments for level-2 incidents (physical conflicts) contained 11 emotion words in the anger, 238 in the disgust, 13 in the fear, 39 in the sadness, 1 in the surprise, 228 in the good, and 31 in happiness categories. The corresponding proportions were 2.3%, 49.0%, 2.7%, 8.0%, 0.2%, 46.9% and 6.4%. The number of emotion words in the 945 comments about level 3 incidents (injuries) was 24 for anger, 494 for disgust, 44 for fear, 130 for sadness, 11 for surprise, 481 for good, and 111 for happy, corresponding to 2.5%, 52.3%, 4.7%, 13.8%, 1.2%, 50.9%, and 11.7%, respectively. The number of emotion words in the 616 comments about level 4 incidents (fatalities) was 21 was for anger, 423 for disgust, 47 for fear, 125 for sadness, 3 for surprise, 427 for good, and 82 for happiness, corresponding to 3.4%, 68.7%, 7.6%, 20.3%, 0.5%, 69.3%, and 13.3%. Therefore, it was concluded that there were more "disgust" and "good" emotion words than other emotion words in all doctor-patient disputes.

Results of manual sentiment value calculation on extracted comment data

Based on the equations for the sentiment value of comments in different situations, we manually assigned sentiment values to the collected comments on doctor-patient dispute incidents. In the process of manually calculating the assigned values, we corrected the shortcomings of the machine algorithm and manually changed or eliminated emotion words that were analyzed incorrectly. For example, the word "Caineng" in the Chinese expression is used as an adjective meaning "knowledge and ability" and as an adverb indicating that one is able to do something. Therefore, after the machine recognized it, we manually verified and corrected it based on the context of the comment. The final scores of the comments for the different levels of incidents were follows: The total score of the 1608 comments about level 1 incidents (verbal conflicts) was -2651. The score of the 486 comments about level 2 incidents (physical conflicts) was -333. The score of the 959 comments about level 3 incidents (injuries) was -1061, and the score of the 616 comments about level 4 incidents (fatalities) was -642. The results of the manual assignment of comment score data are shown in Table 5.

SPSS 26.0 was used for analysis of the comment data because they were found to be nonnormally distributed ($P < 0.05$). The nonparametric Kruskal-Wallis *H* test was used to compare differences between groups of variables. The results of this analysis are shown in Table 6.

As shown in Table 6, the variables positive, negative, disgust, fear, sadness, good, and happy, as well as the comment scores at the four levels of incidents, all show a significant difference between the groups of the levels ($P < 0.05$). This means that there was a significant difference between at least 2 groups of incident comments at the four different levels of incident comments. For the positive variable, differences observed between level 2 incidents and level 1 incidents, between level 2 incidents and level 4 incidents, between level 3 incidents and level 1 incidents, and between level 3 incidents and level 4 incidents were significant. For the negative variable, significant differences were observed between level 2 incidents and level 1 incidents, between level 2 incidents and level 4 incidents, between level 3 incidents and level 1 incidents, and between level 3 incidents and level 4 incidents. For the disgust variable, significant differences were observed between level 2 and level 4 incidents, level 2 and level 1 incidents, level 3 and level 4 incidents, and between level 4 and level 1 incidents. For the fear variable, significant differences were observed between level 2 and level 4 incidents, between level 2 and level 1 incidents, between level 3 and level 4 incidents, and between level 3 and level 1 incidents. For the sadness variable, significant differences were observed between level 2 and level 3 incidents, between level 2 and level 4 incidents, between level 1 and level 3 incidents, between level 1 and level 4 incidents, and between level 3 and level 4 incidents. For the good variable, significant differences were observed between level 3 and level 1 incidents, between level 3 and level 4 incidents, between level 2 and level 1 incidents, and between level 2 and level 4 incidents. For the happy variable, significant differences were observed between level 2 and level 3 incidents, between level 2 and level 4 incidents, and between level 1 and level 4 incidents. For comment scores, significant differences were observed between level 1 and level 3 incidents, between level 1 and level 4 incidents, and between level 1 and level 2 incidents.

Table 4 Example of partial results of Python extracting the number of emotion words corresponding to the matrix data

Serial number	Comments	Length	Positive	Negative	Anger	Disgust	Fear	Sadness	Surprise	Good	Happy
1	It ends 80% of the time with an apology, the nurse showing under-standing, and ending up at home for the rest of the year	14	1	0	0	0	0	0	0	1	0
2	If they can't be punished severely; similar things will keep happening	10	0	0	0	0	0	0	0	0	0
3	Looking at the injuries, it feels like they may not be able to return home next New Year's Eve, either	10	0	1	0	1	0	0	0	0	0
4	Why? I wouldn't accept an apology if I were you	10	1	0	0	0	0	0	0	1	0

Table 5 Example of partial results for the corresponding matrix data after commenting on the manual assignment

Serial number	Comments	Length	Positive	Negative	Anger	Disgust	Fear	Sadness	Surprise	Good	Happy	Comment score
1	Excessive people are inexplicable	5	0	2	0	2	0	0	0	0	0	-8
2	The point is, you can't leave an emergency room unattended	7	0	0	0	0	0	0	0	0	0	0
3	What is an emergency? What is an urgent case? The family's in a hurry, the doctor doesn't panic	12	1	1	0	1	0	0	0	0	1	-3
4	A few doctors have some really bad attitudes	6	0	1	0	1	0	0	0	0	0	-3
5	Doctor, you have to know what an emergency is. Every second counts, understand?	14	1	0	0	0	0	0	0	1	0	5

Because the data were continuous and nonnormally distributed, we performed Spearman's correlation analysis to examine correlations. A binary variable correlation matrix was constructed to show the associations between incident levels, the number of words for each sentiment, and comment scores (Table 7). The results of the correlation analysis revealed that incident level was negatively correlated with the number of emotion words for disgust and positively correlated with both the number of words for sadness and comment scores. The positive variable was positively correlated with negative disgust, sadness, surprise, good, and happy emotion word counts as well as comment scores. The negative variable was positively correlated with the number of emotion words for anger, fear, sadness, good, and happiness and negatively correlated with comment scores. Comment scores were positively correlated with incident level and the number of emotion words for positive, good, and happy and negatively correlated with the number of emotion words for negative, anger, disgust, fear, and sadness.

Multiple stepwise regression analysis were conducted using the comment score as the dependent variable and the incident level and the number of words for each sentiment as independent variables. The results are shown in Table 8. The number of emotion words for negative, anger, disgust, fear, and sadness directly influenced the comment score, and the number of emotion words for incident, positive, surprise, good, and happy indirectly influenced the comment score.

DISCUSSION

This study examined the emotional words in the comments on media reports of doctor-patient disputes at various levels of severity and found that "good" and "disgust" were the most common emotions. Specifically, words that indicated 'disgust' accounted for greatest proportion of emotional words, followed by 'good' emotional words, and emotional words that indicated other meanings accounted for a smaller proportion of emotional words. The results show that in comments on doctor-patient disputes, the public evaluated the good and bad aspects of both sides of the incident based on the content of the report and commented on the incident with a certain tendency according to the specific situation. For the emotional words that express "disgust" in the comments of media reports, the public's evaluation of the object of concern was mainly focused on medical institutions (hospitals), the main fault side of doctor-patient disputes. Comments

Table 6 Kruskal-Wallis *H* test

Variable	Comparison of incident levels		SE	*P* value
Positive	Group differences	14.822		0.002
	2 *vs* 1	113.738	48.270	0.018
	2 *vs* 4	-177.112	56.576	0.002
	3 *vs* 1	83.643	38.222	0.029
	3 *vs* 4	-147.016	48.289	0.002
Negative	Group differences	35.397		0
	2 *vs* 1	218.660	50.200	0
	2 *vs* 4	-281.295	58.838	0
	3 *vs* 1	140.349	39.750	0
	3 *vs* 4	-202.985	50.219	0
Anger	Group differences	1.779		0.619
Disgust	Group differences	27.043		0
	2 *vs* 4	-165.943	56.332	0.003
	2 *vs* 1	182.248	48.062	0
	3 *vs* 4	-143.057	48.080	0.003
	3 *vs* 1	159.362	38.057	0
Fear	Group differences	21.502		0
	2 *vs* 4	-78.824	25.924	0.002
	2 *vs* 1	84.332	22.118	0
	3 *vs* 4	-51.862	22.127	0.019
	3 *vs* 1	57.370	17.514	0.001
Sadness	Group differences	44.747		0
	2 *vs* 3	-81.824	31.089	0.008
	2 *vs* 4	-187.128	33.791	0
	1 *vs* 3	-55.240	22.829	0.016
	1 *vs* 4	-160.543	26.391	0
	3 *vs* 4	-105.304	28.841	0
Surprise	Group differences	5.539		0.136
Good	Group differences	14.396		0.002
	3 *vs* 1	98.017	37.044	0.008
	3 *vs* 4	-147.035	46.800	0.002
	2 *vs* 1	95.630	46.782	0.041
	2 *vs* 4	-144.648	54.831	0.008
Happy	Group differences	9.647		0.022
	2 *vs* 3	-57.709	28.480	0.043
	2 *vs* 4	-94.158	30.956	0.002
	1 *vs* 4	-49.162	24.176	0.042
Comment score	Group differences	14.206		0.003
	1 *vs* 3	-81.270	40.833	0.047
	1 *vs* 4	-104.633	47.204	0.027
	1 *vs* 2	-177.166	51.567	0.001

1: Level 1 incidents (verbal conflicts); 2: Level 2 incidents (physical conflicts); 3: Level 3 incidents (injuries); 4: Level 4 incidents (fatalities).

Table 7 Spearman's correlation analyses between incident levels, number of words for each sentiment and comment scores

Variable	Incident level	Positive	Negative	Anger	Disgust	Fear	Sadness	Surprise	Good	Happy	Comment score
Incident level	1.000										
Positive	0	1.000									
Negative	-0.010	0.101[b]	1.000								
Anger	0	0.028	0.197[b]	1.000							
Disgust	-0.0340[a]	0.104[b]	0.842[b]	0.058[b]	1.000						
Fear	-0.027	0.025	0.262[b]	-0.020	0.048[b]	1.000					
Sadness	0.086[b]	0.047[b]	0.366[b]	0.046[b]	0.072[b]	0.023	1.000				
Surprise	-0.008	0.122[b]	0.015	0.020	0.021	-0.023	-0.003	1.000			
Good	-0.007	0.905[b]	0.094[b]	0.026	0.094[b]	0.027	0.047[b]	0.039[a]	1.000		
Happy	0.027	0.390[b]	0.069[b]	0.026	0.073[b]	0.009	0.042[a]	0.036[a]	0.092[b]	1.000	
Comment score	0.036[b]	0.223[b]	-0.470[b]	-0.070[b]	-0.488[b]	-0.064[b]	-0.099[b]	0.014	0.228[b]	0.041[b]	1.000

[a]$P < 0.05$ (two-tailed).
[b]$P < 0.05$ (two-tailed).

Table 8 Linear regression analysis

Variable	Step 1		Step 2	
	β	SE	β	SE
Incident level	0.020	0.059		
Positive	0.452	2.372		
Negative	-1.084[c]	0.648	-1.009[c]	0.730
Anger	0.136[c]	0.743	0.131[c]	0.838
Disgust	0.304[b]	0.644	0.302[b]	0.725
Fear	0.193[c]	0.667	0.189[c]	0.750
Sadness	0.295[c]	0.632	0.300[c]	0.713
Surprise	-0.035	2.475		
Good	-0.017	2.371		
Happy	-0.094	2.366		
Adjusted R^2	0.460		0.309	
F	312.274[c]		327.572[c]	

[b]$P < 0.01$.
[c]$P < 0.001$.

on the relevant content mainly focused on the following points: Criticism of. the negligence and malpractice of the medical profession; questioning or denouncing the regularity and safety of hospitals and the legitimacy of diagnostic and therapeutic means; condemning the violence of patients against the medical profession; harshly reproaching and resenting those who injured medical practitioners; demanding that the relevant public prosecutors and law enforcement agencies be severely punished; accusing the healthcare system of being inadequate and criticizing the shortcomings of the healthcare system. For the emotional words that expressed "good" in the comments on the media coverage of the incident, the public's evaluation was more focused on solidarity with the injured side in the specific doctor-patient dispute incident. The main content included a positive emotional tendency to call for respect for the facts, respect for both

doctors and patients, and praise of the outcome of the incident. Our findings are consistent with those of Zhao *et al*[25].

In this study, for the variables positive, negative, disgust, fear, sadness, good and happy, as well as the comment scores for the four levels of incidents, the difference between the groups was significant ($P < 0.05$); that is, there was a significant difference between at least 2 groups of incident comments at the four different levels of incident comments. Based on the results of the Spearman correlation analysis, it can be concluded that the comment score is positively correlated with the number of words of emotion, such as incident level, positive, good and happy, and negatively correlated with the number of emotion words, such as negative, anger, disgust, fear and sadness. Positive, good, and happy all denote positively inclined (positive) emotional significance, and negative, anger, disgust, fear, and sadness all denote negatively inclined (derogatory) emotional significance, indicating that the higher the comment score, the stronger the positive inclination of the comment and the weaker the negative inclination. The incident level was negatively correlated with the number of words of disgust and positively correlated with the number of words of sadness and the comment scores, which indicates that more severe the doctor-patient dispute was, the more serious the casualties were. The number of the disgust emotion words in the comments were relatively lower, the number of sadness emotion words were relatively higher, and the scores of the incident comments were higher. A possible. reason was a higher incidence level was associated with more severe injury. the comments about such incidents had fewer words that were biased remarks of a bad nature and more emotional, such as expressing regret and sadness for the injured side. Another possible reason is that with the continuous development and progress of information networks and social media, fragmentation of information and the emergence of tragedies caused by cyber violence, cultural quality continues to improve, people view issues related to doctor-patient incidents with greater emphasis on factual content, and their comments are more peaceful. For example, a level 4 incident was "Net rumors that a doctor in Chongqing was stabbed by a member of patient's family while on duty and died." Comments on this incident included "Doctors cause heartache for others, and doctors with medical ethics and medical style are admired and respected," "Saved countless lives and died such a tragic death! Sad!" The content of their comments reflected the public's pity and grief for the casualties in the incident. The results of this study confirmed Hypothesis two. There was a positive correlation between the level of the incident and the number of words of sadness (*i.e.* the tendency of the public to feel pity and sadness for the victim) in the comments. The incident level was positively correlated with comment scores and the positive variable was positively correlated with a number of words such as negative, disgust, sadness, surprise, good, and happy. The negative variable was positively correlated with a number of words such as anger, disgust, fear, sadness, good, and happy because positive = happy + good + surprise, negative = anger + sadness + fear + disgust. Therefore, as the severity of the incident increased, the severity and influence of the faulty behavior of the incident bearer increased, the heated nature of public comments about doctor-patient disputes intensified, the number of comments published increased, and the proportion of positive and negative emotional tendencies in the comments increased with the increase in the number of comments. Another possible reason is that in the early stage of the media reports, which involves the comments of affected public figures, the severity of the incident, and the public level of education and cultural quality, a more severe doctor-patient dispute may trigger the majority of the public to make overly radical remarks that condemn the behavior of the doctor or patient. In such situations, there is a strong tendency towards negative emotions in the comments. With continuous reporting of the incident, the public will come to view the incident more rationally and participate in the discussion after the outcome of the incident is announced. The negative emotions in the comments then changed to positive emotions and the public expressed more praise for the outcome of the incident and expectations for the future development of the doctor-patient relationship. Thus, the proportion of comments expressing positive emotion was increased and the final score of the incident comments was higher. The study results confirm hypothesis 1 that the comment scores of doctor-patient dispute incidents were related to the level of the incident (*i.e.* the severity of the damage caused by the behavior of the responsible at-fault side).

Based on the results of multiple stepwise regression analysis, it can be concluded that the number of negative emotion words, such as anger, disgust, fear, and sadness directly influenced the comment score, and the number of emotion words for incident level, positive, surprise, good, and happy may have indirectly influenced the score. The intensity of the negative emotions brought about by negative emotion words and their direct impact on the incident comments can be determined. The results of this study confirm hypothesis 3: The intensity of negative emotions brought about by negative emotion words in comments has a direct effect on incident comment scores and opinion influence. The reasons for this intense negative emotional sentiment may be as follows. First, the doctor-patient relationship is often tense, and with the rise of social media and networking platforms, there is a subtle influence on the content of comments. According to a survey by the China Medical Doctors Association, an average of 66 medical disputes occurs per hospital per year in mainland China, and more than 30% of doctors have experienced violence from patients and their families. Secondly, media reports about doctor-patient disputes at all levels and comments from public figures can influence the orientation of public opinion towards such disputes on online social platforms. This includes emotional expressions that come from various sources such as ordinary public users, official news media, social media, and influential online bloggers. When subjects express their views and facts regarding doctor-patient disputes, they may often have personal, subjective impressions, which could include intense emotional tendencies such as anger, disgust, fear, and sadness. Additionally, they may excessively criticize various parties involved, including the medical side, patient side, hospital side, or other relevant institutions. In a level 2 incident a "woman experienced infusion pain, argued with hospital staff angrily, smashed items in the infusion room, and slapped the security guard immediately after the attack." The comments included the following text: "Do not know the sky and the earth. I truly think that who what spoiled you" and "Habitually arrogant and domineering, this time she was taught a well-deserved lesson." The content of the comments was based on one side of the argument and blamed the other side, and thus did not have a rational view of the incident. Therefore, we suggest introducing laws and regulations that follow a top-level design in order to create a favorable social environment for improving tense doctor-patient relationships[26]. Second, the verbal comments of the media should be

regulated at all levels, with guidance provided by public figures and the media. Third, enhancing doctors' education level, boosting their confidence, and earning patients' trust, alleviating their work pressure, and nurturing their sense of professional identity and social responsibility are crucial objectives[27].

CONCLUSION

There was a significant difference between the comment score and the number of partial emotion words for the comments about different levels of doctor-patient disputes. The comment score was positively correlated with the level of the incident and the number of positive emotion words such as, good, and happy and negatively correlated with the number of negative emotion words such as, anger, disgust, fear, and sadness. As the severity of the incident increased, the number of words with positive emotional tendencies increased. Furthermore, as the number of reports about the incident results increased, the public comments became more rational, the number of words with negative emotional tendencies decreased, the negative tendency of the comments gradually changed to a positive tendency, and the scores of the comments increased.

The number of emotion words for negative, anger, disgust, fear, and sadness directly influenced comment scores, and the number of emotion words for incident, positive, surprise, good, and happy may have indirectly influenced the comment scores. The comment scores of incidents were more strongly influenced by emotional words related to negative emotional tendencies.

By applying text sentiment analysis to specific cases of doctor-patient disputes, we extracted the sentiment of comments made by the public. Understanding the emotional differences between doctors and patients has practical significance for establishing harmonious doctor-patient relationships and for guiding the development of positive public opinion on doctor-patient incidents in society.

FOOTNOTES

Author contributions: Lu JR, Wei YH, and Sun JJ designed the research study (substantial contributions to the conception); Lu JR, Wei YH, Wang X, Zang YQ, and Shao JY collected and extracted data; Lu JR analyzed data, and interpreted the data for the work; Sun JJ provided guidance for statistical analysis and provided financial support; the authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy; Lu JR and Wei YH wrote the manuscript; Lu JR, Wei YH, Wang X, Zang YQ, Shao JY, and Sun JJ reviewed the manuscript; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Prospective Study

Predictive value of intracranial high-density areas in neurological function

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Abstract

BACKGROUND

Intracranial high-density areas (HDAs) have attracted considerable attention for predicting clinical outcomes; however, whether HDAs predict worse neurological function and mental health remains controversial and unclear, which requires further investigation.

AIM

To investigate the predictive value of intracranial HDAs for neurological function and mental health after endovascular treatment.

METHODS

In this prospective study, 96 patients with acute ischemic stroke (AIS) who accepted endovascular mechanical thrombectomy (EMT) were included. The enrolled patients underwent cranial computed tomography (CT) examination within 24 hours after EMT. Clinical data in terms of National Institutes of Health Stroke Scale (NIHSS), the 3-month modified Rankin Scale (mRS), self-rating depression scale (SDS), and self-rating anxiety scale (SAS) scores were collected and compared between patients with HDAs and non-HDAs and between patients with good and poor clinical prognosis.

RESULTS

Compared to patients without HDAs, patients with HDAs presented severe neurological deficits (admission NIHSS score: 18 ± 3 *vs* 19 ± 4), were more likely to have post-stroke disabilities (mRS < 3: 35% *vs* 62%), and suffered more severe depression (SDS score: 58 ± 16 *vs* 64 ± 13) and anxiety disorder (SAS score: 52 ± 8 *vs* 59 ± 10). Compared to patients with a good prognosis, patients with a poor prognosis presented severe neurological deficits (admission NIHSS score: 17 ± 4 *vs* 20 ± 3), were more likely to have HDAs on CT images (64% *vs* 33%), and suffered more severe depression (SDS score: 55 ± 19 *vs* 65 ± 11) and anxiety (SAS score: 50 ± 8 *vs* 58 ± 12). Multivariate analysis revealed that HDAs were independent nega-

tive prognostic factors.

CONCLUSION
In conclusion, HDAs on CT images predicted poor prognosis and severe depressive and anxiety symptoms in patients with AIS who underwent EMT.

Key Words: Acute ischemic stroke; Endovascular mechanical thrombectomy; High-density areas; Depressive disorder; Anxiety disorder

Core Tip: High-density areas (HDAs) have great potential in predicting clinical outcomes in patients with acute ischemic stroke (AIS). This prospective study focused on the association of intracranial HDAs with neurological function and mental health after endovascular mechanical thrombectomy for AIS. Through comprehensive evaluation of National Institutes of Health Stroke Scale, the 3-month modified Rankin Scale, self-rating depression scale, and self-rating anxiety scale scores, our study demonstrated that intracranial HDAs on computed tomography images predict poor prognosis and severe depressive and anxiety symptoms.

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INTRODUCTION

Acute ischemic stroke (AIS), with high morbidity, disability, and mortality rates, has become one of the most common causes of death in China in recent years. The lifetime risk of stroke in China is estimated to be 39.3%, ranking first in the world[1]. Moreover, the highest risk is 41.1% in males and 36.7% in females[1]. Intracranial large-artery occlusion in AIS, especially in the anterior circulation, occurs with a high disability rate and severe complications such as stroke-related pneumonia, bedsores, and even death, ultimately leading to a heavy economic burden on households. Over the past three decades, the age-standardized morbidity and mortality rates of stroke have decreased in China, but the stroke burden remains substantial[2].

Early revascularization is key to the treatment of AIS. Endovascular mechanical thrombectomy (EMT) is a safe and effective method for treating AIS resulting from large-artery occlusions[3]. In clinical practice, intracranial high-density areas (HDAs) are observed in patients who undergo initial (within 24 hours) computed tomography (CT) after EMT, with an incidence of 31.2%-60%[4]. Most HDAs are caused by contrast leakage, and a few are caused by intracerebral hemorrhage or a combination of both[4]. Recent studies have suggested that intracranial HDAs after vascular recanalization may indicate a poor prognosis[5-7]. However, one study showed that the occurrence of HDAs was not related to prognosis[4]. The reasons for the association between HDAs and ineffective recanalization are unknown, but the presence of HDAs may indicate blood–brain barrier injury and dysfunction after reperfusion[8].

Although the occluded artery is recanalized, and blood flow is restored after EMT, not all patients with arterial recanalization have good clinical outcomes. This study aimed to investigate the relationship between the occurrence of intracranial HDAs on CT images and clinical outcomes after EMT in anterior circulation cerebral infarctions.

MATERIALS AND METHODS

Patient selection

A total of 96 patients with acute anterior circulation ischemic stroke who underwent EMT at the Ganzhou People's Hospital, China, between January 2022 and December 2023 were included. The inclusion criteria were as follows: (1) Patients admitted to the intensive care unit for ≥ 3 days; (2) patients with AIS in the anterior circulation within 24 hours of onset who underwent endovascular intervention; and (3) patients who provided informed consent for participation in the study. The exclusion criteria were as follows: (1) Cerebral infarction caused by other causes, such as vasculitis; (2) age < 14 years; (3) pregnant or lactating females; (4) concurrent multi-site cerebral infarction; (5) patients with intracranial space-occupying lesions; (6) patients with incomplete data collection due to various factors; and (7) patients in other clinical trials or studies.

Procedures and assessments

This prospective cohort study included patients with AIS who required endovascular thrombectomy due to occlusion or

stenosis of large arteries in the anterior circulation. All patients underwent cranial CT (Philips Healthcare, Best, The Netherlands/Artis zee ceiling, Siemens Healthcare, Erlangen, Germany) examination within 24 hours after EMT and were subsequently divided into HDA and non-HDA groups. Baseline data, including age, sex, risk factors, and routine stroke scales, including the National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin Scale (mRS), were compared between the two groups. The mRS was used to assess clinical prognosis at 3 months, with a good prognosis defined as an mRS score < 3. The self-rating depression scale (SDS) and self-rating anxiety scale (SAS) were used to assess the severity of depressive and anxiety disorders, respectively, and were compared between the non-HDA and HDA groups. According to the mRS score, patients were divided into the good prognosis group (mRS score 0-3) and the poor prognosis group (mRS score 4-6) at 3 months. The HDA, SDS, and SAS scores were compared between the two groups to determine the role of HDAs in clinical outcomes.

Statistical analysis

This prospective cohort study was a triple-blind study. Continuous variables are presented as mean ± SD. Categorical variables are presented as frequencies and percentages, *n* (%). Differences in the continuous variables and the categorical variables were examined with student's *t*-test and the chi-square or Fisher exact test, respectively. The Wilcoxon rank-sum test was used to compare multiple samples of categorical variables and McNemar's test was used to compare two paired samples of continuous variables. Multivariate logistic regression analysis was used to determine the correlation between variables and clinical outcomes. Statistical significance was set at $P < 0.05$. All data were collected using Epidata 3.0, and statistically analyzed using SPSS software (version 13.0).

RESULTS

Patients with or without HDAs on CT images post-EMT

In this study, a triple-blind design was adopted. All patients with acute anterior circulation ischemic stroke underwent cranial CT within 24 hours after EMT. They were divided into non-HDA and HDA groups according to CT image outcomes. Among the 96 patients included in this study, 46 (48%) had non-HDAs (Figure 1A) and 50 (52%) had HDAs on CT images (Figure 1B-D).

Patient prognosis in the presence or absence of HDAs

The clinical characteristics of patients in the non-HDA and HDA groups are shown in Table 1. The mRS was used to assess patient prognosis at 3 months. No significant differences were observed in the baseline data between the two groups ($P > 0.05$). Compared to patients with non-HDAs, those with HDAs presented a higher admission NIHSS score ($P = 0.047$). Among the 46 patients with non-HDAs, 16 had a poor prognosis, while 31 of 50 patients with HDAs had a poor prognosis (mRS < 3: 35% *vs* 62%, $P = 0.001$).

HDAs in patients with good or poor prognosis

Based on the clinical outcomes at 3 months, patients were divided into good and poor prognosis groups. The clinical characteristics of the patients in the two groups are shown in Table 2. No significant differences were observed in the baseline data between the two groups ($P > 0.05$). Poor prognosis was observed in 47 (49%) of the 96 patients in the study. Compared to patients with a good prognosis, those with a poor prognosis presented a higher admission NIHSS score ($P = 0.007$) and were more likely to have HDAs on CT images (64% *vs* 33%, $P = 0.0.004$). Based on the results of multivariate logistic regression analysis, HDAs on CT (OR = 0.326; 95%CI: 0.253-0.323, $P = 0.002$) were independently associated with a poor prognosis.

Depressive and anxiety disorders among patients after EMT

SDS and SAS were used to assess the severity of depressive and anxiety disorders, respectively, in patients with and without HDAs and in patients with good or poor prognosis who accepted EMT. Compared to patients with non-HDAs, patients with HDAs were likely to have more severe depression ($P = 0.015$) and anxiety ($P = 0.032$) (Table 3). Moreover, compared to patients with a good prognosis, those with a poor prognosis had more severe depressive (SDS score: 55 ± 19 *vs* 65 ± 11, $P = 0.021$) and anxiety (SAS score: 50 ± 8 *vs* 58 ± 12, $P = 0.044$) disorders (Table 3).

DISCUSSION

This study aimed to investigate the predictive value of HDAs on CT images for neurological function and mental health after EMT in patients with AIS. These findings suggest that the presence of HDAs predicts severe clinical prognosis and depressive and anxiety symptoms.

AIS is a common cerebrovascular disease with high disability and mortality rates and a low cure rate. To treat AIS, it is essential to restore perfusion to the ischemic brain tissue and protect the function of brain cells. EMT is a safe and effective method for treating AIS with large-artery occlusion. However, numerous studies have demonstrated that although endovascular therapy improves recanalization rates (defined as an mRS score < 3 at 3 months), only approximately 50% of patients have a good prognosis[9-13]. Approximately 50% of patients have poor outcomes, which can be explained by ineffective recanalization after EMT (mRS score > 3 at 3 months), despite recanalization of blood vessels

Table 1 Clinical characteristics of patients in the non-high-density areas and high-density areas groups, *n* (%)

	non-HDAs (*n* = 46)	HDAs (*n* = 50)	*P* value
Age (years, mean)	63 ± 10	67 ± 14	0.683
Gender (male)	25 (54)	26 (52)	0.869
Hypertension	20 (43)	23 (46)	0.453
Hyperlipidemia	5 (11)	7 (14)	0.879
Diabetes mellitus	8 (17)	10 (20)	0.648
Heart disease	24 (52)	27 (54)	0.872
Admission NIHSS score (mean)	18 ± 3	19 ± 4	0.047
mRS score < 3	16(35)	31 (62)	0.001

mRS: Modified Rankin Scale; HDAs: High-density areas; NIHSS: National Institutes of Health Stroke Scale.

Table 2 Clinical characteristics of patients in the good prognosis and poor prognosis groups, *n* (%)

	Good prognosis (*n* = 49)	Poor prognosis (*n* = 47)	*P* value
Age (years, mean)	65 ± 11	67 ± 16	0.878
Gender (male)	26 (53)	25 (53)	0.889
Hypertension	22 (45)	21 (45)	0.552
Hyperlipidemia	6 (12)	6 (13)	0.879
Diabetes mellitus	7 (14)	11 (23)	0.068
Heart disease	26 (53)	25 (53)	0.872
Admission NIHSS score (mean)	17 ± 4	20 ± 3	0.007
HDAs presence	16 (33)	30 (64)	0.004

HDAs: High-density areas; NIHSS: National Institutes of Health Stroke Scale.

Table 3 Self-rating depression scale and self-rating anxiety scale scores of patients in the non-high-density areas and high-density areas groups

	non-HDAs (*n* = 46)	HDAs (*n* = 50)	*P* value
SDS score	58 ± 16	64 ± 13	0.015
SAS score	52 ± 8	59 ± 10	0.032
	Good prognosis (*n* = 49)	Poor prognosis (*n* = 47)	
SDS score	55 ± 19	65 ± 11	0.021
SAS score	50 ± 8	58 ± 12	0.044

HDAs: High-density areas; SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

with a blood flow grade after thrombolytic therapy for cerebral infarction > grade 2b[14]. Intracranial HDAs are observed on follow-up CT of patients after EMT with an incidence of 31.2%-60%[4]. Chen *et al*[7] retrospectively analyzed the clinical treatment of 82 patients with AIS due to anterior circulation large-artery occlusion and showed that the presence of HDAs on C-arm CT scans immediately after EMT resulted in ineffective recanalization, suggesting a poor prognosis. However, An *et al*[15] reported that the presence or absence of HDAs on dual-energy CT scans within 12-24 hours of EMT was not related to clinical outcomes. Whether HDAs predict poor prognosis remains controversial and more extensive research is needed.

In this study, we explored the association between HDAs and neurological function, as well as mental health in patients with AIS after EMT. Based on the CT images, patients were divided into groups with and without HDAs. There were no significant differences in the baseline data including age, sex, and risk factors, whereas the routine stroke scales

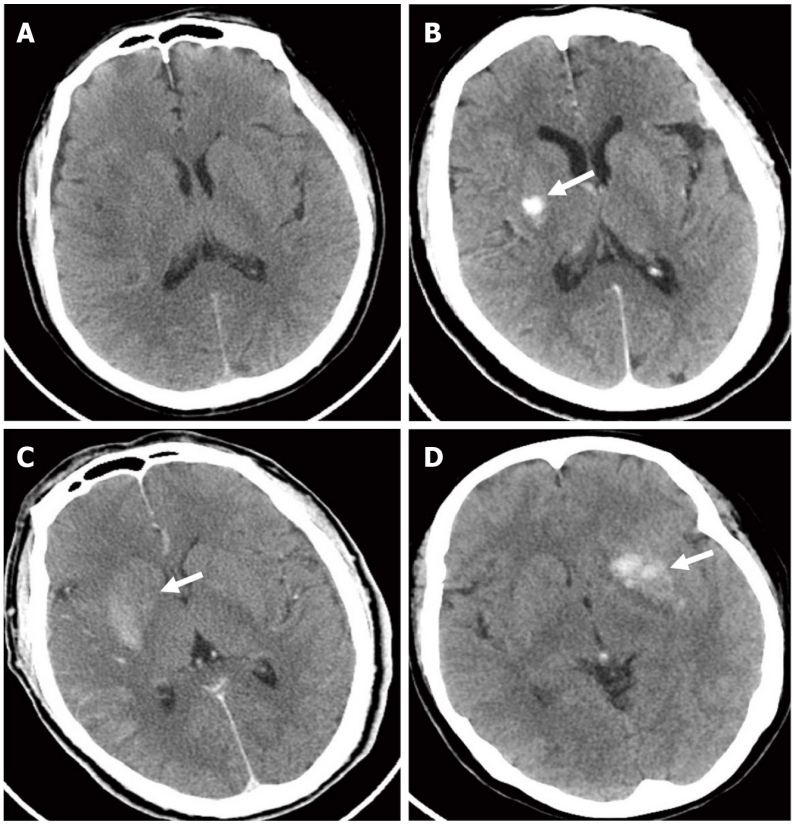

Figure 1 Computed tomography images of non-intracranial high-density areas and high-density areas. A: Computed tomography (CT) image post-endovascular mechanical thrombectomy (EMT) shows no high-density areas (HDAs) in a patient with an admission National Institutes of Health Stroke Scale (NIHSS) of 15 and 3 month modified Rankin Scale (mRS) of 0; B: CT image post-EMT shows right basilar ganglia HDA in a patient with an admission NIHSS of 16 and 3 month mRS of 0; C: CT image post-EMT shows right basilar ganglia and cortical HDAs in a patient with an admission NIHSS of 24 and 3 month mRS of 6; D: CT image post-EMT shows left basilar ganglia HDA in a patient with an admission NIHSS of 25 and 3 month mRS of 6.

including admission NIHSS and 3 month-mRS were significantly different between the two groups. Compared to patients without HDAs, those with HDAs presented a higher admission NIHSS score, suggesting severe neurological deficits. Three months after EMT, patients with HDAs were more likely to have post-stroke disabilities, with an mRS score < 3. The SDS and SAS scores at 3 months were significantly higher in patients with HDAs than in those without HDAs, indicating that the presence of HDAs suggests depression and anxiety severity. Moreover, according to the definition of good prognosis with an mRS score < 3 at 3 months, patients were divided into good and poor prognosis groups. The results indicated that patients with a poor prognosis presented with severe neurological deficits, were more likely to have HDAs on CT images, and had more severe depressive and anxiety disorders than patients with a good prognosis. Multivariate analysis showed that the presence of HDAs was an independent negative prognostic factor in patients with AIS. The potential mechanism of the relationship between HDAs and poor prognosis may be related to failed recanalization. HDAs were observed in approximately 25% of patients with AIS following EMT[5]. Previous studies reported that HDAs are related to an increased risk of symptomatic intracerebral hemorrhage and to unfavorable clinical outcomes[5,6,16-18]. Poor outcomes may be attributed to unsuccessful reperfusion hemorrhage[6,19,20]. To the best of our knowledge, this is the first study on the association between HDAs and the mental health of patients with AIS who received EMT. The underlying mechanism remains unclear and further studies are required to clarify this mechanism.

Although our findings suggest that the presence of HDAs predict a severe clinical prognosis and depressive and anxiety symptoms, this study had two limitations. First, thrombectomy devices, procedural techniques, timing of postoperative CT re-examination, and definition of HDAs varied across studies, which probably led to different results in different studies. Second, the present study included a small sample size and was performed at a single center. Therefore, the current findings cannot be generalized to all patients with acute anterior circulation ischemic stroke who received intravascular reperfusion therapy, which needs to be confirmed in large-scale and multicenter clinical studies.

CONCLUSION

In summary, the presence of HDAs on CT images predicts poor prognosis despite successful EMT. Moreover, the presence of HDAs indicates severe depressive and anxiety symptoms. These findings may serve as a reference for clinicians during the treatment of AIS.

FOOTNOTES

Author contributions: Lai JX and Huang JR analyzed the data; Xie SH contributed new reagents/analytic tools; Lai ZH designed the research; Lu ZJ wrote the paper.

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ORIGINAL ARTICLE

Randomized Clinical Trial

Effects of hormone replacement therapy on mood and sleep quality in menopausal women

Qing Liu, Zhen Huang, Ping Xu

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Abstract

BACKGROUND

Hormone replacement therapy is an effective treatment strategy for the management of symptoms in naturally menopausal women. However, some patients report experiencing adverse effects.

AIM

To analyze the effects of hormone replacement therapy in menopausal female patients.

METHODS

A total of 152 menopausal female patients admitted to the Gynecology Department of the Ganzhou Maternal and Child Health Hospital between January 2021 and December 2023 were divided into the observation group (n = 76, conventional treatment + hormone replacement therapy) and the control group (n = 76, conventional treatment only) *via* random casting. The improvement observed in the following items were compared between the groups: Kupperman menopausal index (KMI), emotional state [The Positive and Negative Affect Scale (PANAS)], sleep quality [Self-Rating Scale of Sleep (SRSS)], treatment effectiveness, and treatment safety.

RESULTS

The modified KMI and SRSS scores of the observation group were lower than those of the control group after three rounds of treatment. The improvement in the PANAS score observed in the observation group was greater than that observed in the control group ($P < 0.05$). The total treatment effectivity rate in the observation group was higher than that in the control group (86.84% *vs* 96.05%, $\chi^2 = 4.121$, $P = 0.042$). The incidence rate of adverse reactions in the two groups was comparable (6.58% *vs* 9.21%, $\chi^2 = 0.361$, $P = 0.547$).

CONCLUSION
Hormone replacement therapy effectively improved the clinical symptoms, actively channeled negative emotions, and improved the quality of sleep in menopausal patients, indicating its effectiveness and safety.

Key Words: Hormone replacement therapy; Menopause; Women; Mood states; Sleep quality; Sex hormones

Core Tip: Menopausal females can benefit from hormone replacement therapy; however, this treatment may increase the risk of venous thrombosis, cardiovascular disease, and breast cancer.

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INTRODUCTION

Menopause, a normal part of the aging process in women, is characterized by changes in the hormone levels, biochemical environment, and psychological state of the patients. Menopause heralds the gradual decline of ovarian function resulting in the complete disappearance of ovarian function. If not diagnosed and treated in a timely manner, menopause affects the physiological and psychological health of the patients and interferes with their daily life and work[1]. Conventional treatment strategies encompassing psychological, diet, exercise, and other interventions have exhibited beneficial effects in relieving physical and mental stress. However, achieving the desired effect *via* the application of these strategies alone is difficult in clinical practice[2]. Hormone replacement therapy is a therapeutic method that involves the administration of synthetic hormones to treat the symptoms caused by insufficient hormone secretion. This method can effectively relieve the discomfort associated with menopausal symptoms[3]. However, previous studies have shown[4] that the overall effect of hormone replacement therapy cannot meet the expectations of women who have been menopausal for > 10 years or those aged > 60 years; moreover, it also significantly increases the absolute risk of coronary heart disease, venous thromboembolism, and dementia. Clinical reports on the use of hormone replacement therapy in menopausal women are controversial. Therefore, 152 menopausal women were randomly included in the present study and analyzed to further elucidate the benefits and drawbacks of hormone replacement therapy.

MATERIALS AND METHODS

General information

This study was approved by the Medical Ethics Committee of the Ganzhou Maternal and Child Health Hospital. The patients and their family members were provided with a detailed explanation regarding the objective of the study. Informed consent was obtained prior to commencing the study. In accordance with the random throw method, 152 menopausal patients admitted to the Department of Gynecology of the Ganzhou Maternal and Child Health Hospital between January 2021 and December 2023 were divided into the control (n = 76) and observation (n = 76) groups. The characteristics of the two groups were compared to detect statistically significant differences (P > 0.05; Table 1).

The inclusion criteria were as follows: Patients with available laboratory, imaging, and other comprehensive assessment results who met the disease determination criteria[5]; patients with natural menopause persisting for > 6 months; patients who had not received hormone drug therapy 3 months before enrollment; and voluntary participation, with the provision of written informed consent.

The exclusion criteria were as follows: History of allergy, history of malignant disease or serious organic injury, history of mental disorder or mental illness, and declined/withdrawn participation.

Methodology

The patients in the control group received conventional treatment, *i.e.* psychological adjustment. The patients were guided to relax their bodies and minds *via* rhythmic deep breathing and encouraged to express their true inner thoughts and concerns. The concerns of the patients were considered and appropriate verbal encouragement and action support were provided. The importance and necessity of maintaining a good state of mind were explained to the patients *via* positive and negative case education. Patients presenting with serious psychological symptoms were offered professional psychological counseling. In addition to these measures, the patients were encouraged to cultivate hobbies and interests and actively participate in social activities.

Table 1 Comparison of baseline information between the two groups

Baseline information		Control, *n* = 76	Observation, *n* = 76	t/χ^2	*P* value
Age in years		55.02 ± 4.05	54.59 ± 4.26	0.638	0.525
Disease duration in years		3.86 ± 1.14	4.12 ± 1.30	1.311	0.192
Body mass index in kg/m^2		24.87 ± 0.95	25.04 ± 0.92	0.121	0.264
Educational level	High school and below	49 (64.47)	45 (59.21)	0.446	0.504
	Above high school	27 (35.53)	31 (40.79)		

Data are mean ± SD or *n* (%).

Dietary adjustment: The patients were instructed to consume < 300 mg of cholesterol, < 6 g of salt, ≤ 50 g of sugar, ≤ 15 g of alcohol, and 1000 mg of calcium per day. In addition, they were also instructed to drink 1500-1700 mL of water per day and consume fresh fruits and vegetables; foods high in calcium, such as fish, meat, eggs, and milk; and high-fiber or whole-grain foods.

Exercise management: The patients were encouraged to perform regular physical activities, such as 150 minutes of moderate-intensity aerobic exercise per week. In addition, the patients were recommended to perform activities, such as cycling, swimming, square dancing, walking, jogging, or yoga, according to their strength, while paying attention to the gradual progress. Muscle training exercises were added according to the needs of the patient.

Medication guidance: Medications, such as antidepressants and melatonin receptor agonists, were administered according to the needs of the patient. Strict compliance with the use of medications was ensured.

In addition to the interventions: The patients in the observation group also received hormone replacement therapy. Estradiol valerate tablets (0.5 mg; Beijing Union Pharmaceutical Factory; State Drug Permit H20000031) were administered orally at a dose of 1 mg once a day for 14 days. Multiple modes of administration were available; however, oral ingestion of estradiol valerate tablets is predominantly utilized for the supplementation of estrogen deficiency associated with either natural or surgical menopause. Consequently, the present study employed the oral route for drug administration. In addition to administering estradiol valerate tablets on the 15th day, hydroxyprogesterone acetate tablets (0.25 g; Beijing Slippery Pharmaceuticals Ltd; State Drug Permit H11021562) were administered orally at a dose of 8 mg once a day for 14 days. The treatment cycle comprised three courses (28 days). Detections were conducted within 3 days post-therapy conclusion.

Observation indicators

Improvement in symptoms (before treatment *vs* after three courses of treatment). The modified Kupperman menopausal index (KMI) score[6] was used to evaluate 13 items: Hot flashes and sweating (0-12 points), sensory abnormalities (0-6 points), insomnia (0-6 points), moodiness (0-6 points), depression (0-3 points), vertigo (0-3 points), osteoarthralgia/muscle pain (0-3 points), headache (0-3 points), fatigue (0-3 points), palpitations (0-3 points), sexuality (0-3 points), crawling sensation of the skin (0-3 points), urological sensations (0-3 points), and skin pain (0-3 points). The total score ranged from 0 to 63 points, with a higher score indicating more severe symptoms.

Emotional state (before treatment *vs* after three courses of treatment): The Positive and Negative Affect Scale (PANAS) score[7] is a scale comprising two dimensions (positive and negative emotions). Each dimension consists of 10 adjectives; each adjective was scored on a 5-point Likert scale (1-5 points). The emotional state of the patient was positively correlated with the score obtained.

Quality of sleep (before treatment *vs* after three courses of treatment): The Self-Rating Scale of Sleep (SRSS) score[8], which contains the following 10 items, was used to assess the quality of sleep. Insufficient duration of sleep, poor quality of sleep, insufficient sleep/wakefulness, duration of sleep, difficulty falling asleep, disturbed sleep, early rising, dreaming/nightmares/night terrors, medication use, attitude toward sleep, and physiological and psychological reactions to insomnia. Minimum and maximum values of 1 point and 5 points, respectively, were assigned to each item. A higher score indicated a poorer quality of sleep.

Treatment effectiveness: Resolution of symptoms after three courses of treatment and a reduction in the modified KMI score of at least 80% was defined as cure. Significant improvement in the clinical symptoms after three courses of treatment, and a reduction in the modified KMI score of 50%-80% was defined as a significant effect. Reduction in the clinical symptoms after three courses of treatment, and a reduction in the modified KMI score of 20%-50% was defined as effective treatment. No reduction in the clinical symptoms after three courses of treatment, and a reduction in the modified KMI score of < 20% was defined as ineffective treatment[9]. The overall treatment effectiveness rate was calculated as the sum of the cure, significant, and effective rates.

Treatment safety: The incidence of adverse reactions (*e.g.*, nausea and vomiting, breast swelling and pain, and irregular vaginal bleeding) in the two groups was recorded.

Statistical analysis

All statistical analyses were performed using SPSS27.0 software. The normality of data distribution was determined. Normally distributed data were compared between the groups using independent samples *t*-test. Intra-group differences were evaluated using the paired samples *t*-test. Counts are presented as the percentage rate (%) and were evaluated using the χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of symptom improvement between the two groups

The modified KMI scores of the two groups were well-balanced before treatment, with no statistically significant differences ($P > 0.05$). The modified KMI scores of the two groups decreased after three courses of treatment. The magnitude of the decrease in the observation group was greater, and the difference was statistically significant ($P < 0.05$). Table 2 presents further details.

Comparison between the emotional states of the two groups

The scores obtained for each dimension of the PANAS score by the two groups were well-balanced before treatment, and the difference was not statistically significant ($P > 0.05$). The PANAS scores of the two groups improved after three courses of treatment. The magnitude of the improvement in the observation group was greater, and the difference was statistically significant ($P < 0.05$). Table 3 presents further details.

Comparison between the sleep quality of the two groups

The SRSS scores of the two groups were well-balanced before treatment, with no statistically significant differences ($P > 0.05$). The SRSS scores of the two groups decreased after three courses of treatment. The magnitude of the decrease in the observation group was greater, and the difference was statistically significant ($P < 0.05$). Table 4 presents further details.

Comparison between treatment effectiveness observed in the two groups

Comparison of the total treatment effectiveness rates of the two groups revealed that the rate of the observation group was higher, and the difference was statistically significant (86.84% *vs* 96.05%, $\chi^2 = 4.121$, $P = 0.042$). Table 5 presents further details.

Comparison between the safety of treatment observed in the two groups

The incidence of adverse reactions did not significantly differ between the groups (6.58% *vs* 9.21%, $\chi^2 = 0.361$, $P = 0.547$). Table 6 provides further details.

DISCUSSION

Epidemiological data[10] shows that the prevalence of menopause and menopausal symptoms in the reproductive, menopausal transition, and postmenopausal stages is 9.3%, 23.9%, and 21.5%, respectively. Menopause is a physiological process that women must undergo. The occurrence of menopause is mainly related to the gradual depletion of follicles in the ovaries caused by a significant decline in female hormones. Poor lifestyle habits also promote the occurrence of menopause to a certain extent[11]. Conventional treatment can regulate the psychological state of patients and encourage them to consciously adopt behaviors that are beneficial. However, its effect on improving their condition is relatively limited. Hormone replacement therapy is an effective treatment strategy for the management of symptoms in naturally menopausal women. Thus, its use for the management of menopause has been recognized and endorsed. However, some patients report experiencing breast distension and pain, vaginal bleeding, and other discomforts, which are associated with certain adverse effects to an extent[12,13].

The dysfunction of the hypothalamic-pituitary-ovarian axis owing to the decrease in estrogen levels results in an imbalance in neurotransmitter, cytokine, and hormone levels, thereby inducing menopause. The findings of the present study demonstrated that the reduction in the KMI score of the observation group was greater than that in the control group after three courses of treatment ($P < 0.05$). This may be attributed to the following reasons: Estradiol valerate is an estrogenic drug administered as a part of hormone replacement therapy. It can increase the estrogen levels and improve menopausal symptoms, regulate the reproductive and endocrine systems to further maintain ovarian function, and delay the progression or avoid further deterioration of the disease. Medroxyprogesterone acetate is a progestational hormone drug that can inhibit the secretion of gonadotropin-releasing hormone in the hypothalamus *via* reverse feedback. Furthermore, it can reduce the luteinization of the anterior pituitary gland. Methylprogesterone acetate is a progestin that can inhibit the secretion of hypothalamic gonadotropin-releasing hormone *via* reverse feedback, reduce the secretion of luteinizing hormone in the anterior pituitary gland, and regulate the secretion of estradiol in the ovary to influence the physiological activities of the reproductive system. These actions have a positive effect on the alleviation of menopausal

Table 2 Comparison of symptom improvement between the two groups

Content	Time	Control, *n* = 76	Observation, *n* = 76	*t* value	*P* value
Hot flashes and sweating	Pre-treatment	8.35 ± 1.27	8.20 ± 1.32	0.714	0.476
	Post-treatment	4.24 ± 1.18[a]	3.78 ± 1.09[a]	2.496	0.014
Abnormal sensations	Pre-treatment	3.52 ± 0.47	3.43 ± 0.50	1.143	0.255
	Post-treatment	2.05 ± 0.36[a]	1.93 ± 0.24[a]	2.418	0.017
Insomnia	Pre-treatment	3.23 ± 0.61	3.35 ± 0.58	1.243	0.216
	Post-treatment	2.14 ± 0.43[a]	1.98 ± 0.32[a]	2.602	0.010
Agitation	Pre-treatment	3.12 ± 0.45	3.03 ± 0.37	1.347	0.180
	Post-treatment	1.69 ± 0.28[a]	1.60 ± 0.15[a]	2.470	0.015
Depression	Pre-treatment	1.87 ± 0.36	1.90 ± 0.42	0.473	0.637
	Post-treatment	1.15 ± 0.19[a]	1.09 ± 0.10[a]	2.436	0.016
Vertigo	Pre-treatment	1.41 ± 0.29	1.38 ± 0.27	0.660	0.510
	Post-treatment	1.01 ± 0.17[a]	0.95 ± 0.08[a]	2.784	0.006
Bone and joint pain/muscle pain	Pre-treatment	1.93 ± 0.35	1.87 ± 0.40	0.984	0.327
	Post-treatment	1.31 ± 0.22[a]	1.24 ± 0.09[a]	2.567	0.011
Headaches	Pre-treatment	1.61 ± 0.53	1.58 ± 0.60	0.327	0.744
	Post-treatment	1.02 ± 0.34[a]	0.90 ± 0.23[a]	2.549	0.012
Fatigue	Pre-treatment	1.73 ± 0.42	1.68 ± 0.37	0.779	0.437
	Post-treatment	1.19 ± 0.30[a]	1.08 ± 0.24[a]	2.496	0.014
Palpitations	Pre-treatment	1.49 ± 0.38	1.52 ± 0.43	0.456	0.649
	Post-treatment	0.83 ± 0.25[a]	0.74 ± 0.19[a]	2.499	0.014
Crawling sensation of the skin	Pre-treatment	1.17 ± 0.26	1.22 ± 0.30	1.098	0.274
	Post-treatment	0.73 ± 0.18[a]	0.67 ± 0.10[a]	2.540	0.012
Sexuality	Pre-treatment	3.47 ± 0.58	3.38 ± 0.61	0.932	0.353
	Post-treatment	2.03 ± 0.35[a]	1.90 ± 0.24[a]	2.671	0.008
Urinary tract infection	Pre-treatment	3.02 ± 0.49	3.06 ± 0.54	0.478	0.633
	Post-treatment	1.88 ± 0.36[a]	1.75 ± 0.27[a]	2.518	0.013

[a]*P* < 0.05 compared with this group before treatment.
Data are mean ± SD.

Table 3 Comparison between emotional states observed in the two groups

Group	*n*	Positive emotions		Negative emotions	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control	76	20.45 ± 5.23	32.79 ± 5.46[a]	34.58 ± 5.69	22.81 ± 5.37[a]
Observation	76	20.59 ± 5.37	35.08 ± 5.54[a]	34.23 ± 5.72	20.64 ± 5.15[a]
t value		0.163	2.567	0.378	2.543
P value		0.871	0.011	0.706	0.012

[a]*P* < 0.05 compared with this group before treatment.
Data are mean ± SD.

Table 4 Comparison between sleep quality of the two groups

Group	*n*	Insufficient sleep		Poor quality of sleep		Insufficient sleep or wakefulness		Sleep duration		Difficulty in sleeping	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control	76	3.47 ± 0.81	2.21 ± 0.53[a]	2.91 ± 0.67	2.08 ± 0.35[a]	3.08 ± 0.72	2.39 ± 0.48[a]	2.84 ± 0.52	2.02 ± 0.31[a]	2.69 ± 0.40	1.77 ± 0.24[a]
Observation	76	3.52 ± 0.79	2.02 ± 0.38[a]	2.88 ± 0.70	1.96 ± 0.23[a]	3.11 ± 0.69	2.22 ± 0.31[a]	2.90 ± 0.57	1.91 ± 0.24[a]	2.73 ± 0.46	1.69 ± 0.15[a]
t value		0.385	2.540	0.270	2.498	0.262	2.594	0.678	2.446	0.572	2.464
P value		0.701	0.012	0.788	0.014	0.793	0.010	0.499	0.016	0.568	0.015

[a]$P < 0.05$ compared to this group before treatment.
Data are mean ± SD.

Table 5 Comparison of treatment effectiveness between the two groups

Group	*n*	Curable	Conspicuous effect	Efficiently	Null	Overall effectiveness of treatment
Control	76	20 (26.32)	29 (38.16)	17 (22.37)	10 (13.16)	66 (86.84)
Observation	76	24 (31.58)	30 (39.47)	19 (25.00)	3 (3.95)	73 (96.05)
χ^2						4.121
P value						0.042

Data are *n* (%).

Table 6 Comparison between treatment safety in the two groups

Group	*n*	Nausea and vomiting	Breast swelling and pain	Irregular vaginal bleeding	Incidence of adverse reactions
Control	76	2 (2.63)	1 (1.32)	2 (2.63)	5 (6.58)
Observation	76	2 (2.63)	3 (3.95)	2 (2.63)	7 (9.21)
χ^2					0.361
P value					0.547

Data are *n* (%).

symptoms. The findings of the present study are consistent with the those of the study Armeni *et al*[12].

Abnormal secretion of sex hormones, often accompanied by increased psychogenic anxiety, emotional instability, and irritability, is observed in menopausal women. In addition to symptoms of depressed mood, somatic symptoms, such as menopausal somatic discomfort, and autonomic dysfunction have also been reported[14]. Previous studies have shown [15] that women experiencing menopause are prone to developing sleep disorders (16%-47% and 35%-60% in perimenopausal and postmenopausal women, respectively) and that they mainly present with symptoms of insomnia with or without anxiety or low depression and mood disorders. The findings of the present study demonstrated that the SRSS scores were generally lower in the observation group and that the PANAS scores were significantly higher in the observation group after three courses of treatment ($P < 0.05$). This may be attributed to hormone replacement therapy gradually restoring the sex hormone secretion level, which can help in maintaining a stable mood and prevent and control the occurrence of tossing, turning, and sleeplessness owing to emotional excitement and anxiety. Thus, hormone replacement therapy can effectively alleviate negative mood and sleep disorders.

The data presented in Tables 5 and 6 show that the total treatment effectiveness rate and incidence of adverse reactions in the observation group were 96.05% and 9.21%, respectively. This may be attributed to hormone replacement therapy compensating for the insufficient secretion of sex hormones in menopausal women and targeting the discomfort caused by the symptoms related to menopause. Nevertheless, commencing hormone replacement therapy can result in breast swelling and pain, vaginal bleeding, and other adverse reactions. Therefore, clinicians must be careful with the use of these drugs and take measures to avoid excessive accumulation of estrogen or progesterone in the body and increased incidence of tumors and cardiocerebral and cerebral vascular diseases. The findings of the study conducted by Vigneswaran *et al*[15] confirm this view.

CONCLUSION

The application of hormone replacement therapy has a definite effect. It can effectively alleviate the symptoms of menopause and facilitate return to normal life. Thus, it is worthwhile to promote its use. However, hormone replacement therapy is a "double-edged sword". If the harm outweighs the benefits associated with the application of the treatment, it can cause serious adverse consequences and further endanger the patient's daily life and health. Thus, the application of hormone replacement therapy should be commenced after thorough individual risk stratification and assessment. Clinicians should select a suitable treatment plan after judging whether the patient is suitable for treatment by fully weighing the advantages and disadvantages and avoid adverse outcomes.

FOOTNOTES

Author contributions: Liu Q and Huang Z designed the research study; Liu Q, Huang Z, and Xu P performed the primary literature review and data extraction, analyzed the data, and wrote the manuscript; Liu Q and Huang Z revised the manuscript for important intellectual content; All authors have read and approved the final version.

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ORIGINAL ARTICLE

Basic Study

Gastrointestinal problems in a valproic acid-induced rat model of autism: From maternal intestinal health to offspring intestinal function

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Abstract

BACKGROUND

Autism spectrum disorder (ASD) is a developmental disorder characterized by social deficits and repetitive behavior. Gastrointestinal (GI) problems, such as constipation, diarrhea, and inflammatory bowel disease, commonly occur in patients with ASD. Previously, GI problems of ASD patients were attributed to intestinal inflammation and vertical mother-to-infant microbiome transmission.

AIM

To explore whether GI problems in ASD are related to maternal intestinal inflammation and gut microbiota abnormalities.

METHODS

An ASD rat model was developed using valproic acid (VPA). Enzyme-linked immunosorbent assay and fecal 16S rRNA sequencing were used to test GI changes.

RESULTS

VPA exposure during pregnancy led to pathological maternal intestinal changes, resulting in alterations in maternal gut microbiota. Additionally, the levels of inflammatory factors also increased. Moreover, prenatal exposure to VPA resulted in impaired duodenal motility in the offspring as well as increased levels of inflammatory factors.

CONCLUSION
GI problems in ASD may be associated with maternal intestinal inflammation and microbiota abnormality. Future research is required to find more evidence on the etiology and treatment of GI problems in ASD.

Key Words: Autism spectrum disorder; Gastrointestinal problems; Gut microbiota; Intestinal inflammation; Intestinal motility

Core Tip: In previous studies, the etiology and treatment of gastrointestinal (GI) tract disease in autistic patients have not received sufficient attention. Thus, our research focused more on GI problems in autism, and used the valproic acid-induced autism model to explore the relationship of maternal gut microbiota and inflammation with offspring GI problems. In this study, we found that valproic acid exposure during pregnancy was related to pathological maternal intestinal changes and alterations in maternal gut microbiota. Our findings will provide more evidence and possibilities for autism intervention.

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INTRODUCTION

Autism spectrum disorder (ASD) is a chronic developmental disability with social dysfunction and repetitive behaviors [1]. According to data from the Centers for Disease Control and Prevention, 1/36 children under the age of 8 years (approximately 4% of boys and 1% of girls) is estimated to have ASD[2]. Beyond the core symptoms of ASD, many of ASD patients experience other symptoms, including gastrointestinal (GI) dysfunction as well as unusual eating and sleeping habits[3]. GI problems commonly occur in patients with ASD, with up to 70% of patients being affected[4]. Generally, GI problems in ASD mainly include diarrhea, constipation, and abdominal pain[5]. Moreover, GI problems in ASD children with ASD are associated with the severity of behavioral ASD symptoms[6]. GI problems directly affect the quality of life of children with ASD and increase the psychological and economic burden of their families.

Although GI symptoms are common in children with ASD, their etiology remains unknown. It was inferred that the pathogenesis may be related to changes in gut microbiota, increased intestinal permeability, and immune abnormality. The gut microbiota constitutes a special intestinal environment that affects brain development by acting on the nervous, endocrine, and immune systems[7,8]. Intestinal villi deformation and inflammatory cell infiltration were observed in rats with gut dysbiosis[9]. Both clinical and animal studies have shown that alterations in gut microbiota and gut infection are related to ASD. Furthermore, the gut microbiome usually coexists with inflammation and neurotransmitter abnormalities [10-13]. The gut microbiota is also involved in the maturation of the immune system.

Interestingly, evidence has suggested that maternal intestinal problems may be a risk factor for the development of ASD[14-16]. Sadik *et al*[17] found that there was a potential link between maternal inflammatory bowel disease (IBD) and ASD. In animal ASD models, BTBR and SHANK3 mutant mice developed gut microbiome dysbiosis[18,19]. Furthermore, changes in the maternal gut microbiota may promote maternal immune activation-associated ASD model phenotypes [20]. The maternal gut microbiota is vertically transmitted to the offspring, which is important for offspring to establish their metabolic and developmental pathways. Moeller *et al*[21] showed that vertical transmission is not only related to the mode of delivery, but also to the composition of the maternal gut microbiota.

Intestinal homeostasis is maintained by the interaction of the intestinal mucosa, microbiota, nutrients, and metabolites. Gut dysbiosis leads to intestinal disorders[22] and affects the progression of IBD[23]. Furthermore, nonoptimal maternal nutrition during the embryonic period epigenetically affects the fetus, which may induce susceptibility to the development of colitis[24]. These results suggest that an abnormal maternal gut microbiota not only induces maternal gut inflammation but also adversely affects the offspring.

Although evidence has shown that genes that increase the risk of ASD may be associated with maternal intestinal inflammation and microbial dysbiosis, the effects of adverse environmental factors during pregnancy on the maternal and offspring GI tracts remain unclear. To identify the environmental factors that affect the maternal intestinal condition, we created a valproic acid (VPA)-induced ASD rat model to detect changes in maternal intestinal microbiota and inflammation. Additionally, we wanted to determine whether changes in the maternal GI system are associated with GI problems in children with ASD.

MATERIALS AND METHODS

Animal husbandry and care

We obtained Wistar rats (male and female rats, 270-350 g) from the Beijing Vital River Laboratory Animal Technology Co., Ltd. The animals were housed individually in cages with a 12-12 h light-dark cycle. Food and water were provided *ad libitum* from the cage lid. Humidity and temperature were maintained at 50% ± 10% and 23 ± 2 °C, respectively. The study protocol was approved by the Institute of Acupuncture and Moxibustion Animal Care and Use Committee (approval No. Y2023-03-14-02). The United States National Institutes of Health Guide for the Care and Use of Laboratory Animals was followed in this study.

VPA rat model

Female and male rats were mated overnight in the same cage. The day when vaginal plugging occurred was considered as embryonic day 0.5 (E0.5). Pregnant rats were randomized into VPA and control [normal saline (NS)] groups. In the VPA group, pregnant rats were intraperitoneally injected with 450 mg/kg of VPA (Sigma: P4543) on embryonic day 12.5 (E12.5). The control group received the same concentration of NS. On postnatal day 21 (PND 21), same-sex offspring were housed separately (2-6 per cage). Male offspring were used in this study. The timeline of the experiments is shown in Figure 1A.

Tissue preparation

Rats were anesthetized by intraperitoneally injecting 10% chloral hydrate and transcardially perfused with NS. Duodenal and rectal tissues were quickly removed and rinsed with 1X phosphate buffered saline (PBS). After sonicating 100 mg of tissue for 1 min in radioimmunoprecipitation assay lysis buffer (RIPA; Beyotime, China) containing 1:100 protease inhibitor, centrifugation was performed at 12000 *g* for 15 min. Then, the supernatant was removed and stored at -80 °C. We used a BCA Protein Assay kit (Beyotime, China) to measure the total protein concentration of each sample, and the results were interpreted on a BIO-RAD iMark™ micro-plate reader.

Enzyme-linked immunosorbent assay

Before enzyme-linked immunosorbent assay (ELISA), duodenal and rectal tissues were diluted 1:20 and 1:10 with RIPA, respectively. Inflammatory factors [tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6] and neurotransmitters [acetylcholine (ACh) and nitric oxide synthase (NOS)] in duodenal and rectal tissues were detected by ELISA. The standards or samples were pipetted into the wells of microtiter plates containing monoclonal antibodies against the following proteins: TNF-α (CSB-E11987r, CUSABIO), IL-1β (CSB-E08055r, CUSABIO), IL-6 (CSB-E04640r, CUSABIO), ACh (CSB-E08044r, CUSABIO), and NOS (CSB-E14034r, CUSABIO). Substrate solution was added to the wells after washing to remove unbound antibody-enzyme reagent. The enzymatic reactions resulted in a blue product, which turned yellow when phosphoric acid stop solution was added. The concentrations of the factors of interest in the samples were calculated using standard curves as the intensity of the color was directly proportional to the amount of total target protein bound in the first step. The results were calculated as the target protein concentration *vs* total protein.

Hematoxylin & eosin staining

Duodenal and rectal tissues were immersed in 4% paraformaldehyde for 4 h and then transferred to containers containing 70% ethanol. Individual lobes were placed in processing cassettes, dehydrated through a series of alcohol gradients, and embedded in paraffin blocks. Tissue sections measuring 5 μm were deparaffinized in xylene, rehydrated through a series of decreasing concentrations of ethanol, and washed in PBS. They were then stained with hematoxylin & eosin (H&E). Images were taken with a Nikon microscope (ECLIPSE Ni-E, Japan).

Fecal 16S rRNA sequencing and microbial analysis

After the rats were anesthetized, we obtained fecal samples from the rectum. Following fecal collection, total DNA was extracted from fecal samples using the CTAB/SDS method. DNA concentration and purity were monitored by 1% agarose gel electrophoresis. DNA was diluted with sterile water to 1 ng/μL. 16S rRNA genes were amplified with specific primers and barcodes. The cycling conditions included an initial denaturation step at 98 °C (1 min), then 30 cycles of 98 °C (30 s), 50 °C (30 s), and 72 °C (30 s), and a final extension at 72 °C (5 min). The polymerase chain reaction products (containing SYB green) were mixed with loading buffer and electrophoresed on a 2% agarose gel. We used Qiagen Gel Extraction Kit (Qiagen, Germany) to purify the mixed polymerase chain reaction products.

The library was sequenced on an Illumina NovaSeq platform at Novogene Bioinformatics Technology Co., Ltd. (Tianjin, China). For high-quality clean tags, the quality filtering on the raw tags were performed with fastp (version 0.20.0) software. To assess the complexity and differences among samples, we used beta diversity, which was based on weighted and unweighted unifrac distances in QIIME2. Nonmetric multidimensional scaling (NMDS) was performed with QIIME modules and visualized using the R package (version 3.5.2). To investigate the differences in community structure between groups, we used the Adonis and Anosim functions in QIIME2 software. To determine the different species at each taxonomic level, we performed MetaStat and *t*-test analyses with R software (version 3.5.3).

Duodenal motility recording

Duodenal motility recording was performed by PND35-42. To record duodenal motility, we used a rubber condom to create a latex balloon, which was then attached to one tip of a PE-50 tubing. The other end of the tubing was connected to a syringe and a pressure sensor through a tee pipe. The rats were placed in supine position, and a 2-cm incision was made

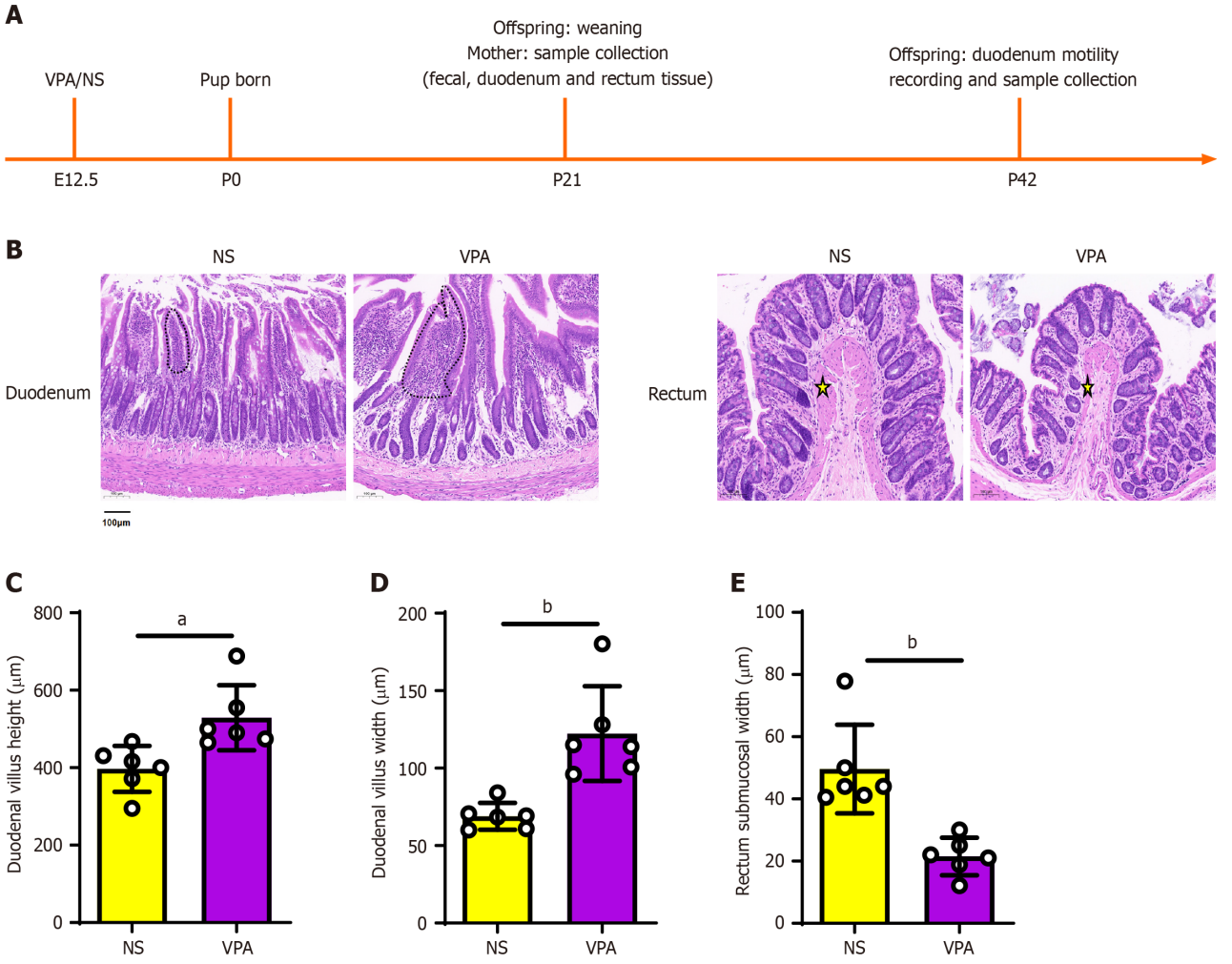

Figure 1 Histological evaluation of intestinal tissue of the normal saline and valproic acid groups (hematoxylin & eosin staining; scale bar = 100 μm; 10 ×). A: Timeline of experimental design; B: Hematoxylin & eosin staining of the duodenum (above) and rectum (down). The duodenal villi are marked by dotted lines. The submucosa is marked by a yellow star; C and D: Histological statistics of duodenal villi height and width; E: Histological statistics of rectal submucosal width. Data are presented as the mean ± SD (normal saline group $n = 6$, valproic acid group $n = 6$). Unpaired t test, $^{a}P < 0.05$, $^{b}P < 0.01$. NA: Normal saline; VPA: Valproic acid.

at the ventral median line 1 cm below the xiphoid process. The abdominal skin, muscle layer, and peritoneum were incised. Another incision was made in the duodenum (1 cm from the pylorus), and the latex balloon was placed. We then sutured the duodenal incision, muscle layer, and skin. Double distilled H_2O was injected into the latex balloon, and duodenal pressure changes were recorded with Spike2V8.02 software.

Statistical analysis

We used IBM SPSS Statistics 19 (SPSS Inc., Chicago, IL, United States) and GraphPad Prism 5.0 (GraphPad Software Inc., San Diego, CA, United States) for statistical analyses and graph generation. All data sets were normality-tested using the Shapiro-Wilk normality test before choosing the statistical test. Statistical significance was assessed by the unpaired Student's t-test and Mann-Whitney U test. Results are expressed as the mean ± standard deviation of the mean (SD), and $P < 0.05$ (two-tailed) was considered statistically significant.

RESULTS

Pathological changes in the duodenum and colon in VPA-induced ASD rats

First, we extracted the duodenal and colonic tissues of mother rats in the VPA and NS groups for H&E staining. H&E staining showed that in the VPA group, the duodenal villi height and width were increased ($P < 0.05$; Figure 1B-D), while the rectal submucosal width was reduced ($P < 0.05$; Figure 1E). These results suggest that VPA exposure during pregnancy affects the maternal intestinal structure.

Effects of VPA exposure during pregnancy on maternal intestinal microbiota

We then explored the differences in gut microbiota between the NS and VPA groups. The Venn diagram displayed 614 unique operational taxonomic unit (OTUs) in the VPA group and 382 in the NS group. Meanwhile, 571 OTUs were shared by the two groups (Figure 2A). NMDS was then conducted to investigate the differences between groups of samples (Figure 2B). When stress was < 0.2, it meant that NMDS accurately reflected the degree of difference between samples. Moreover, the VPA and NS groups displayed different microbial profiles at different levels. Compared with the NS group, populations of gamma-proteobacteria, Rhizobiaceaea, and Proteobacteria were decreased in the VPA group, while some bacterial strains, such as Elusimicrobia and Tuzzerella, were higher in the VPA group (Figure 2C-G). These results further suggest that VPA exposure during pregnancy may alter the composition of the maternal gut microbiota.

VPA exposure during pregnancy increases levels of maternal intestinal inflammatory factors

Next, we used ELISA to evaluate the levels of maternal intestinal inflammatory factors in the VPA and NS groups to determine whether VPA exposure induces maternal intestinal inflammation. The results showed that compared with the NS group, the levels of TNF-α were higher in the duodenum, whereas those of IL-6 and IL-1β were not significantly different, in the VPA group ($P < 0.05$; Figure 3A-C). In rectal tissues of the VPA group, IL-6 levels were higher, whereas there was no significant difference in TNF-α or IL-1β levels ($P < 0.01$; Figure 3D-F). These results indicate that prenatal VPA exposure increases the levels of maternal intestinal inflammatory factors.

Intestinal motility is impaired in offspring in the VPA group

After assessing changes in the maternal gut microbiota and intestinal inflammation, we evaluated intestinal function in offspring in the VPA group. The migrating motor complex (MMC) is a cyclic motility pattern that occurs in the stomach and small bowel during the interdigestive state[25]. MMC can be divided into four phases: Phase I is the quiescent phase with no contractions; phase II is characterized by random contractions; phase III has a sudden onset and ends with a burst of contractions with maximal amplitude and duration; and phase IV is characterized by the rapid decrease of contractions [26]. Phase IV represents a short transition period back to the quiescence of phase I; in this study, we focused on phases I, II, and III. As the duodenum is connected to the pylorus and is responsible for food digestion and absorption, we chose the duodenum to assess intestinal motility during puberty. As shown in Figure 4A-C, the duration of MMC I and II in the VPA offspring group was longer than that of the NS offspring group ($P < 0.001$).

Meanwhile, there was no significant difference between the VPA offspring group and the NS offspring group in the duration of MMC III. Consistent with the duodenal motility results, ACh levels were lower and NOS levels were higher in the VPA offspring group than in the NS offspring group ($P < 0.01$; Figure 4D-E). These results suggest that offspring in the VPA group would develop disorders in duodenal motor function, which might be the reason for GI problems in ASD.

Levels of intestinal inflammatory factors are increased in offspring in the VPA group

Finally, we evaluated intestinal inflammation in offspring in the NS and VPA groups. As expected, the VPA offspring group showed higher levels of intestinal inflammation; the levels of intestinal IL-1β, IL-6, and TNF-α were increased in the duodenum (Figure 5). This suggests that GI problems in patients with ASD may be related to intestinal inflammation.

DISCUSSION

Our findings show that VPA exposure during pregnancy can alter the maternal gut microbiota and increase the levels of inflammatory factors. Furthermore, in offspring of VPA-induced ASD rat models, intestinal motility decreased along with changes in intestinal neurotransmitters, and that levels of intestinal inflammatory factors increased. These results suggest that the maternal intestinal condition is involved in the pathogenesis of ASD. Vertical transmission of the maternal microbiota from mother to infant in ASD is worthy of discussion.

VPA is a drug used to treat epilepsy and mood disorders. Epidemiology has demonstrated that VPA exposure during pregnancy is an important risk factor for the pathogenesis of ASD[27-29]. The mechanism for this may be due to the passage of VPA into the fetus through the placenta. However, there is a lack of evidence on the effects of VPA on changes in the maternal GI system. Through daily feeding, we observed the development of diarrhea in rats after VPA injection. H&E staining also showed that VPA causes changes in the maternal intestinal villi and muscle layers. Kim *et al*[30] also found that the thickness of the GI mucosa and its muscle layers was reduced in offspring of VPA rats. According to our results, exposure to VPA during pregnancy induced intestinal inflammation. Coincidentally, in 2022, a previous study[17] found that there was a potential link between parental, particularly maternal, IBD and ASD in children, and that its results may reflect the influence of the maternal intestinal condition on the prenatal environment. Hence, we hypothesized that the severity of maternal intestinal inflammation might be an important factor in the development of ASD.

Our results demonstrated that the maternal gut microbiota was altered after VPA exposure, which is in line with previous findings. A study found that some symptoms of ASD were associated with specific gut microbiota shared by children and their mothers[17]. Kimura *et al*[31] also showed that the maternal microbiota shaped the metabolic system of offspring in mice. Our findings provide additional evidence for the vertical transmission of maternal gut microbiota and ASD development.

Compared with the NS group, we did not find differences in the overall structure, diversity, or abundance of maternal gut microbiota in the VPA group. However, *t*-test analysis revealed that Elusimicrobia and Tuzzerella populations were higher in the VPA group than in the NS group. Elusimicrobia is a gut-associated bacterial phylum that has a relatively

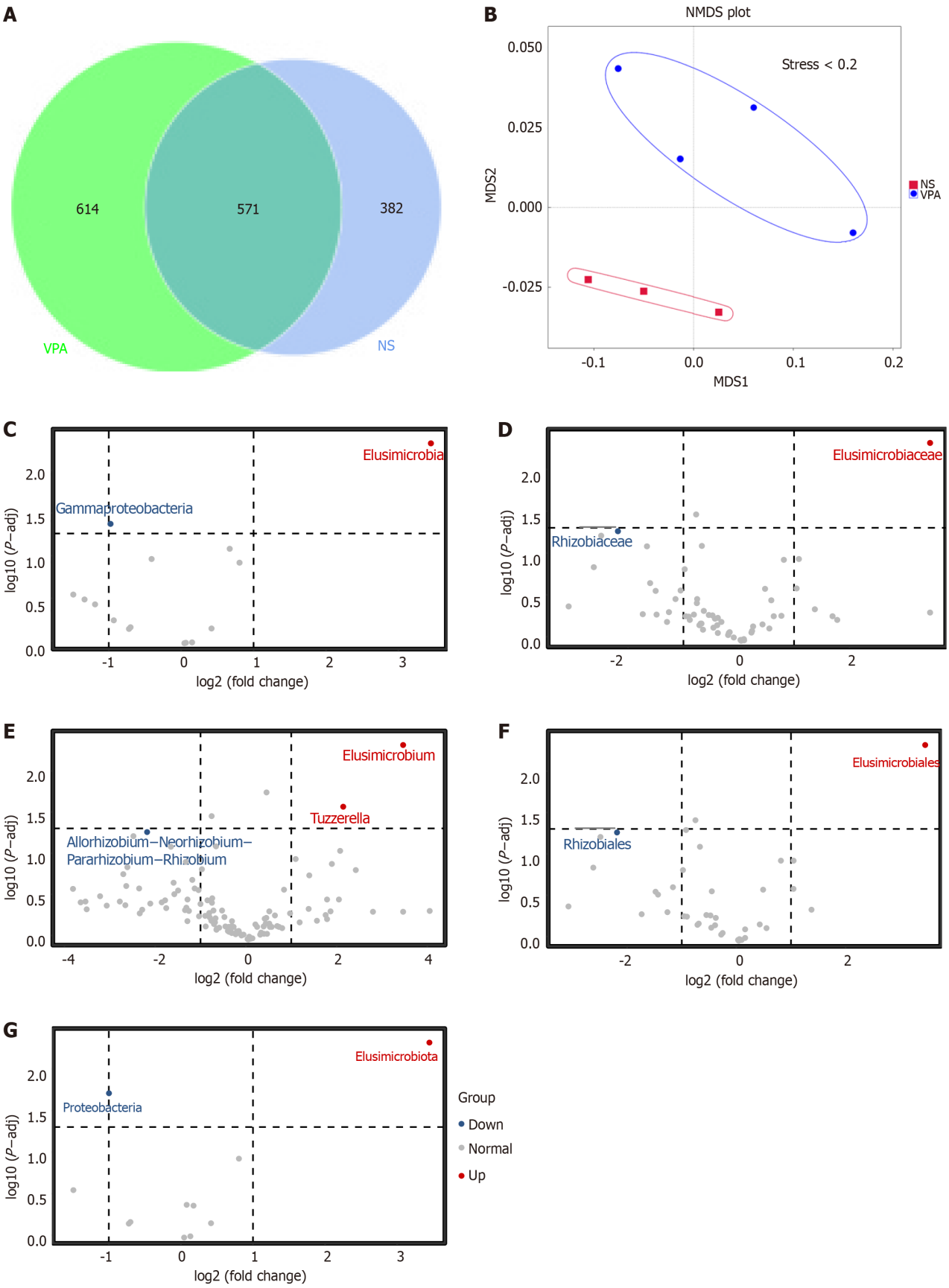

Figure 2 Alteration of gut microbiota in normal saline and valproic acid groups according to 16S rRNA data. A: Venn diagram of observed operational taxonomic units in normal saline and valproic acid (VPA) groups; B: Beta diversity of gut microbiota based on nonmetric multidimensional scaling; C-G: Significantly different species at each taxonomic level (class, family, genus, order, and phylum) based on *t*-test analysis. Normal saline group $n = 3$, valproic acid group $n = 4$. $P < 0.05$. NA: Normal saline; VPA: Valproic acid.

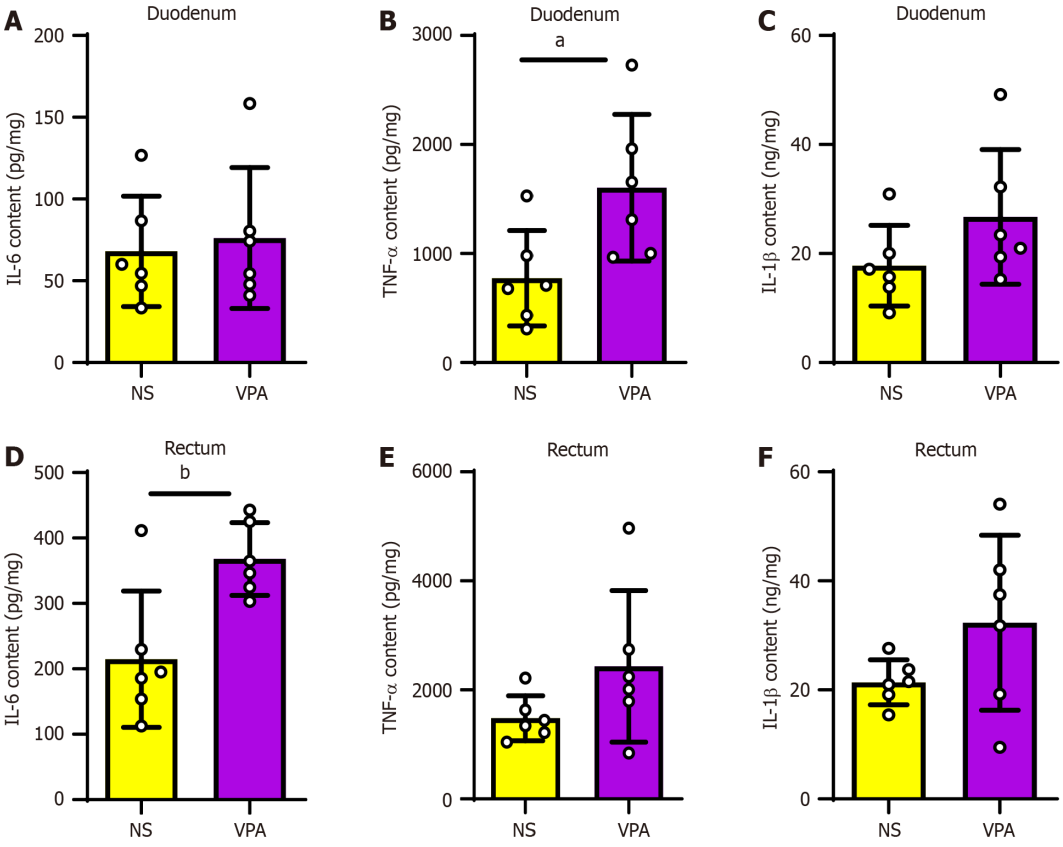

Figure 3 Levels of intestinal inflammatory factors are increased in valproic acid group. A-C: Interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), and IL-1β levels in the duodenum in normal saline (NS) and valproic acid (VPA) groups; D-F: IL-6, TNF–α, and IL-1β levels in the rectum in NS and VPA groups. Data are presented as the mean ± SD (normal saline group $n = 6$, valproic acid group $n = 6$). Unpaired t test, $^{a}P < 0.05$, $^{b}P < 0.01$. TNF-α: Tumor necrosis factor-alpha; IL: Interleukin; NA: Normal saline; VPA: Valproic acid.

small genome. An earlier study reported that Elusimicrobia populations were increased in the intestines of Göttingen minipigs and rhesus macaques after irradiation[32]. Furthermore, Tuzzerella has been demonstrated to grow in different mouse models such as IBD and depression[33,34]. Meanwhile, Proteobacteria populations were decreased in the VPA group. According to a previous review[35], Proteobacteria is a marker for an unstable microbial community. Therefore, from the results of the maternal microbiota analysis in this study, we could infer that VPA exposure during pregnancy alters the maternal gut microbiota and induces inflammation.

Gut microbiota imbalance destroys the intestinal mucosal barrier function, resulting in the entry of bacterial endotoxins and metabolites into the intestinal mucosa and triggering inflammatory responses[36]. The maternal gut microbiota and its inflammatory factors may then be passed to infants through mother-to-child vertical transmission. In line with previous studies[37,38], our results demonstrate that offspring in the VPA group developed GI problems. Meanwhile, in prior studies, the researchers tended to use intestinal permeability to explain GI problems in ASD[39-41]. In this research, we provided new evidence regarding the mechanisms of GI problems in ASD. Similarly, it was reported that Foxp1+/- mice developed GI transit dysfunction[42]. Interestingly, SHANK3 mutant zebrafish also showed GI motility disruption [43]. Hence, GI motility disorders have been observed in multiple animal models of ASD. These results suggest that GI motility should also be considered when treating ASD, and that improving GI motility may be beneficial for improving the core symptoms of ASD.

A widely accepted hypothesis on the development of ASD is excitatory-inhibitory (E-I) ratio imbalance. Most of the evidence for E-I imbalance was obtained from brain regions such as the neocortex, hippocampus, amygdala, and cerebellum[44-46]. For example, an increased E-I ratio in the prefrontal cortex may result in behavioral and social impairments[47]. Meanwhile, the enteric nervous system (ENS) is rich in excitatory and inhibitory neurotransmitters, which can directly act on GI smooth muscle cells. Hence, the ENS is also called the second brain. In this study, our results indicate that ACh levels in the ENS of offspring in the VPA group were decreased, but NOS levels were increased. This phenomenon might partly explain the disorder in intestinal motility and also provide a new perspective on the E-I ratio imbalance in ASD.

Gut dysbiosis and immune alterations are common in children with ASD[48,49]. Gut dysbiosis is related to inflammation and immune activation[50]. Furthermore, the gut microbiota may play an important role in intestinal transit[51]. Thus, our study provides additional evidence on the adverse maternal outcomes of drug exposure and the effects of these adverse outcomes on their offspring. Modulation of the gut microbiota seems to be a promising strategy to ameliorate GI manifestations in ASD, but further studies are warranted.

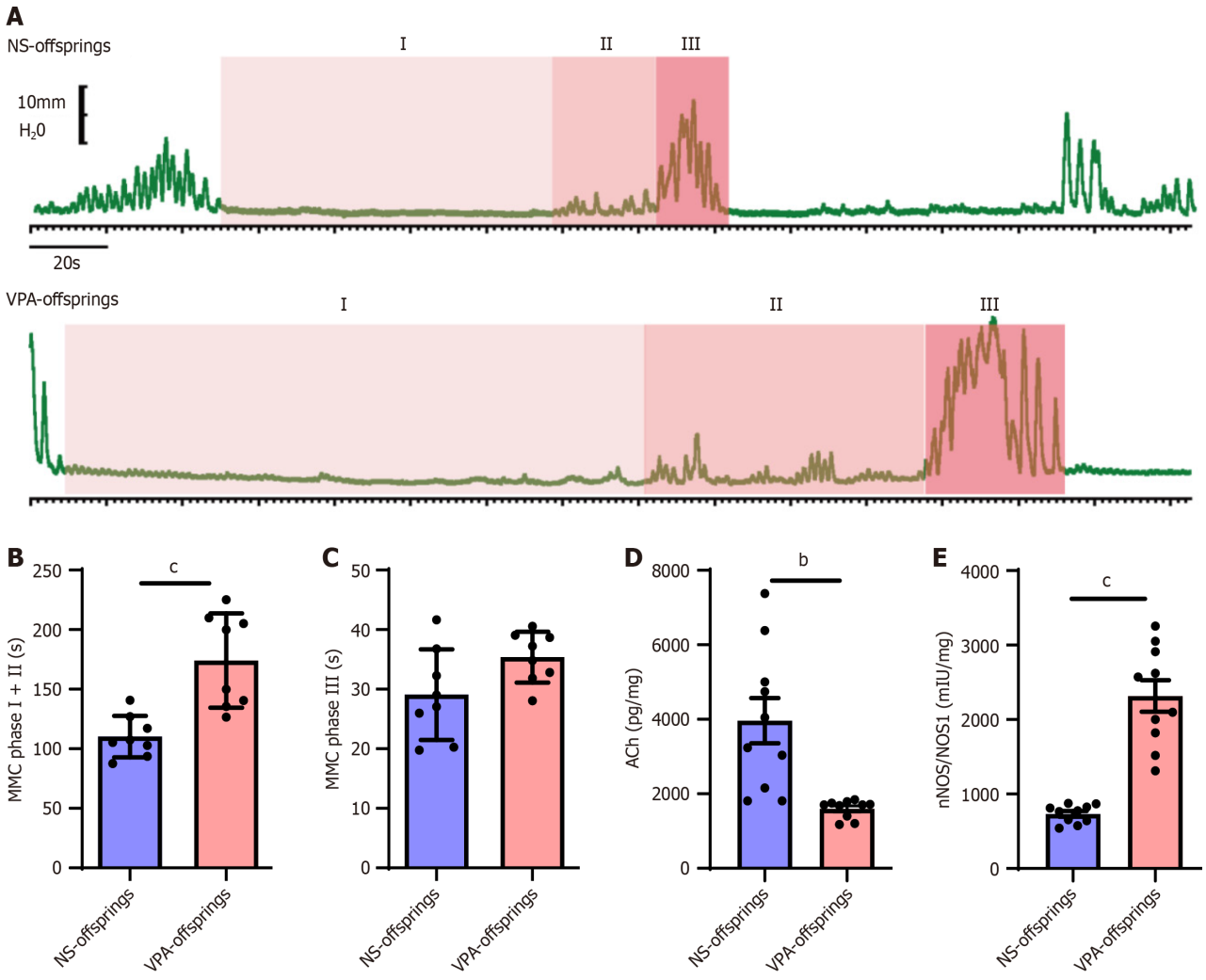

Figure 4 Duodenal motility and neurotransmitters are impaired after prenatal valproic acid exposure. A: Duodenal motility in normal saline (NS) and valproic acid (VPA) offspring at different phases of migrating motor complex (MMC); B and C: Duration of MMC phases I + II (B) and III (C) in NS and VPA offspring groups (NS offspring group n = 8, VPA offspring group n = 8). Unpaired t test, $^{a}P < 0.05$, $^{b}P < 0.01$; D and E: Levels of acetylcholine (D) and nitric oxide synthase (E) in NS and VPA offspring groups in the duodenum. Data are presented as the mean ± SD (normal saline offspring group n = 10, valproic acid offspring group n = 10). Unpaired t test, $^{b}P < 0.01$, $^{c}P < 0.001$. NA: Normal saline; VPA: Valproic acid; MMC: Migrating motor complex; ACh: Acetylcholine; NOS: Nitric oxide synthase.

Currently, studies have been focusing on the gut microbiota to treat GI problems in ASD[52,53]. However, the treatment of GI motility in ASD is rarely reported. As an early therapeutic method, acupuncture has significant benefits in treating GI motility disorders. It was shown that acupuncture can promote GI movement through parasympathetic nerve stimulation[54]. Moreover, acupuncture is also being considered as a potential treatment for ASD[55], with neural plasticity and the brain-gut axis being the postulated mechanisms involved[56,57]. Future studies should pay more attention to the therapeutic effects and mechanisms of acupuncture on GI problems in ASD.

In this study, we only discussed the effects of VPA exposure during pregnancy on the GI system of the mothers and their offspring. A possible limitation of this study is the mechanism of vertical transmission of inflammation and maternal gut microbiota, which should be explored further. Besides, the sample size of this study was limited due to the lack of animal experimental environment. In the future, we will expand the sample size, and hope to discover a therapeutic approach to solve this problem.

CONCLUSION

This study demonstrated that VPA exposure during pregnancy may induce maternal intestinal inflammation and cause gut microbiota abnormalities. Offspring of VPA-induced ASD rat models developed duodenal dysmotility and had increased levels of intestinal inflammatory factors. Further research should be conducted to obtain additional evidence regarding GI problems in ASD as well as to develop effective treatment strategies.

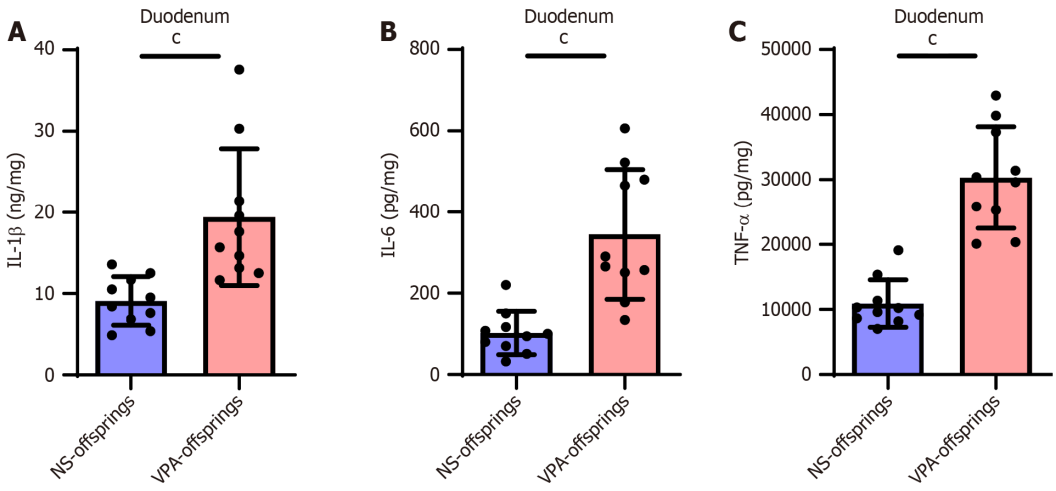

Figure 5 Levels of duodenal inflammatory factors are increased in valproic acid group. A: Interleukin (IL)-1β levels in the duodenum in normal saline (NS) and valproic acid (VPA) groups; B: IL-6 levels in the duodenum in NS and VPA groups; C: Tumor necrosis factor-alpha levels in the duodenum in NS and VPA groups. Data are presented as the mean ± SD (normal saline offspring group $n = 8$, valproic acid offspring group $n = 8$). Unpaired t test, $^cP < 0.001$. TNF-α: Tumor necrosis factor-alpha; IL: Interleukin; NA: Normal saline; VPA: Valproic acid.

FOOTNOTES

Author contributions: Li S and Zhang N contributed to this study equally as co-first authors of this manuscript. Wang XX conceived and designed the study and wrote the manuscript; Li S and Li W performed the experiments and analyzed the data; Zhang HL and Zhang N reviewed and edited the manuscript; and all authors approved the final version.

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META-ANALYSIS

Multimodal abnormalities of brain structures in adolescents and young adults with major depressive disorder: An activation likelihood estimation meta-analysis

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Abstract

BACKGROUND

Major depressive disorder (MDD) in adolescents and young adults contributes significantly to global morbidity, with inconsistent findings on brain structural changes from structural magnetic resonance imaging studies. Activation likelihood estimation (ALE) offers a method to synthesize these diverse findings and identify consistent brain anomalies.

AIM

To identify consistent brain structural changes in adolescents and young adults with MDD using ALE meta-analysis.

METHODS

We performed a comprehensive literature search in PubMed, Web of Science, Embase, and Chinese National Knowledge Infrastructure databases for neuroimaging studies on MDD among adolescents and young adults published up to November 19, 2023. Two independent researchers performed the study selection, quality assessment, and data extraction. The ALE technique was employed to

synthesize findings on localized brain function anomalies in MDD patients, which was supplemented by sensitivity analyses.

RESULTS

Twenty-two studies comprising fourteen diffusion tensor imaging (DTI) studies and eight voxel-based morphometry (VBM) studies, and involving 451 MDD patients and 465 healthy controls (HCs) for DTI and 664 MDD patients and 946 HCs for VBM, were included. DTI-based ALE demonstrated significant reductions in fractional anisotropy (FA) values in the right caudate head, right insula, and right lentiform nucleus putamen in adolescents and young adults with MDD compared to HCs, with no regions exhibiting increased FA values. VBM-based ALE did not demonstrate significant alterations in gray matter volume. Sensitivity analyses highlighted consistent findings in the right caudate head (11 of 14 analyses), right insula (10 of 14 analyses), and right lentiform nucleus putamen (11 of 14 analyses).

CONCLUSION

Structural alterations in the right caudate head, right insula, and right lentiform nucleus putamen in young MDD patients may contribute to its recurrent nature, offering insights for targeted therapies.

Key Words: Major depressive disorder; Adolescent; Young adults; Neuroimaging; Diffusion tensor imaging; Voxel-based morphometry; Activation likelihood estimation; Meta-analysis

Core Tip: This activation likelihood estimation (ALE) meta-analysis illuminates significant structural brain changes in adolescents and young adults with major depressive disorder (MDD), particularly in the right caudate head, right insula, and right lentiform nucleus putamen, highlighting their potential as neural markers. By employing ALE across diffusion tensor imaging and voxel-based morphometry studies, the research reveals consistent patterns of reduced fractional anisotropy, underscoring the recurrent nature of MDD. These insights provide a deeper understanding of its neuropathology and highlights the critical role of specialized neuroimaging in unraveling the complex mechanisms underlying MDD.

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INTRODUCTION

Major depressive disorder (MDD), a complex neuropsychiatric condition characterized by pervasive feelings of sadness, pessimism, heightened sensitivity, and cognitive dysregulation, significantly contributes to the global disease burden across diverse age groups, especially among adolescents and young adults[1]. In the global context, the prevalence of self-reported depressive symptoms in adolescents is approximately 34%, with regions such as the Middle East, Africa, and Asia reporting the highest prevalence of elevated depressive symptoms in this demographic group[2]. In addition, the prevalence of MDD among young people has markedly increased in the past decade[3]. This demographic variation emphasizes the critical need for age-specific research that encompasses both adolescents and young adults to effectively address and understand the nuances of MDD within these populations. Depressive symptoms during these crucial developmental periods are often underrecognized, thus potentially leading to rapid disease progression and long-term detrimental effects on educational attainment, social integration, and overall quality of life[4]. The onset of MDD during these stages of significant biological, psychological, and social transformations introduces unique challenges, thus underscoring the importance of specialized research aimed at elucidating the distinct etiology, pathophysiology, and treatment responses of MDD in adolescents and young adults[5,6].

In recent years, the rapid advancement of neuroimaging research has provided a robust foundation for investigating the neurophysiology of MDD patients. Despite decades of fundamental science, clinical neuroscience, and psychiatric research, the pathophysiology of severe MDD remains incompletely understood[7]. Neuroimaging methods offer a powerful, noninvasive avenue to study the neurobiological mechanisms underlying psychiatric disorders[8]. These neuroimaging techniques have yielded invaluable insights into the impact of depression on brain structures in adolescents and young adults, thus providing insight into the intricate interplay between neural development and psychopathology[9]. Structural magnetic resonance imaging (sMRI) is one such technique that has been pivotal in advancing our understanding of the brain's structure in the context of mental health disorders[10]. sMRI provides high-resolution images of the brain, thus enabling detailed analyses of brain morphology and structure[11]. Within the domain of sMRI, techniques such as voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) have been instrumental[12].

VBM allows for the investigation of focal differences in brain anatomy by comparing the concentration of gray matter across different brain regions, whereas DTI focuses on the integrity and organization of white matter tracts by measuring the diffusion of water molecules in the brain[13].

Although researchers have used sMRI techniques to analyze changes in brain structure in adolescents and young adults with MDD, the findings of these studies are inconsistent and remain controversial[14-35]. This inconsistency underscores the complexity of MDD across these age groups and the influence of individual and methodological differences. The high prevalence and distinct nature of adolescent and young adult MDD necessitate a nuanced understanding of its neural underpinnings. sMRI studies, including those utilizing DTI and VBM, have provided valuable insights into brain structural anomalies associated with MDD[36]. However, the variability in research outcomes highlights the complexity of the disease and the impact of individual and methodological differences[37]. This variability calls for a comprehensive and systematic approach to synthesize existing research, such as by utilizing activation likelihood estimation (ALE) meta-analysis. By integrating a wealth of available data, ALE meta-analysis aims to extract coherent and actionable insights, thus bridging the gap in our understanding of the neural basis of MDD among adolescents and young adults. Importantly, the ALE meta-analysis method overcomes the challenges of method diversity and result heterogeneity, thus helping to screen for credible and practically valuable research results[38]. Previously, Yuan *et al*[39] used the ALE method to conduct a meta-analysis of MDD patients; however, they did not include a young population and may not have identified the consistently vulnerable brain regions in the resting state that may differ between adolescent depression patients and adults.

In this study, we hypothesized that populations with depressive disorders among adolescents and young adults will exhibit distinct brain outcome alteration patterns compared to healthy control (HC) groups, thus potentially revealing neural damage mechanisms associated with depressive disorders. We employed ALE analysis to exclusively focus on multimodal brain structure anomalies by using methodologies from DTI and VBM studies, thus aiming for a more comprehensive understanding of consistent brain structural changes in patients with depressive disorders among adolescents and young adults.

MATERIALS AND METHODS

Literature search

In alignment with PRISMA[40], a comprehensive literature search was systematically executed across four major electronic databases up to November 19, 2023. This review was registered with PROSPERO (ID: CRD42023371521). These databases included PubMed, Web of Science, Embase, and Chinese National Knowledge Infrastructure. The search terms were as follows: (adolescent OR youngster OR young people OR youth OR childhood OR teenage OR teen OR juvenile) AND (depression OR depression neurosis OR depressive disorder OR major depression OR melancholia) AND (white matter OR white brain matter OR cerebellar white matter OR white matter integrity) AND (diffusion tensor* OR DTI OR magnetic resonance imaging OR tractography OR mean diffusivity OR axial diffusivity OR radial diffusivity OR fractional anisotropy OR structural connectivity OR structural changes OR structural MRI OR voxel-based morphometry OR VBM) AND (magnetic resonance OR MRI OR functional MRI OR fMRI OR neuroimaging). In addition, review articles and the reference lists of the included articles were also checked to identify potential omitted studies in the searches.

Inclusion and exclusion criteria

Studies were included in this analysis if they met the following criteria: (1) Had a diagnosis of depression according to the Diagnostic and Statistical Manual of Mental Disorders edition in use at the time of the study's publication; (2) included adolescent or young adult participants; (3) were right-handed; and (4) had results reported for the whole brain in stereotactic space, either in the Montreal Neurological Institute (MNI) or Talairach coordinates for DTI or VBM studies. Studies were excluded if they met at least one of the following criteria: (1) Were abstracts, case reports, systematic reviews, or meta-analyses; (2) were intervention studies; (3) used regional homogeneity or amplitude of low-frequency fluctuations (ALFF); (4) focused on brain connectivity networks or depression in combination with other diseases; or (5) were studies wherein the full text was not available or did not report of coordinates.

To prevent data duplication, when two or more studies used the same dataset, only the study with the largest sample size and most comprehensive information was selected. For longitudinal or intervention studies, only baseline data were considered.

Data extraction

Two authors (H YZ and ZQ) independently extracted data from each study by using a predefined data extraction form. Any disagreements were resolved through discussion among the authors. Information on the authors, publication year, sample size, characteristics of the study population (age and sex), age range, and MRI technical details (MRI scanner, field strength, processing software, standard stereotactic space, method, differential brain region, corrective methods, and thresholds) was obtained (Table 1). The coordinates in each study were independently extracted following the requirements of the ALE.

Quality assessment

The quality of the included studies was assessed by using the Newcastle Ottawa Quality Assessment Scale (NOS). The

Table 1 Characteristics of the included studies

Ref.	Sample size		Age, mean ± SD		Sex, M/F		MRI equipment & field strength	Processing software	Method	Differential brain region	Corrective methods	Quality
	Patient	HCs	Patient	HCs	Patient	HCs						
Cullen *et al*[14], 2010	14	14	16.79 ± 1.29	16.81 ± 1.50	4/10	6/8	Siemens Trio Tim 3.0 T	FSL	DTI	10	NA	4/1/1
Liu *et al*[15], 2010	12	16	Approximately 30.38	Approximately 29.75	4/12	4/12	Siemens 1.5 T	SPM12	DTI	14	$P_{uncor} < 0.001$	4/1/1
Henderson *et al*[16], 2013	17	16	6.80 ± 2.20	16.40 ± 1.40	9/8	6/10	Siemens Allegra 3.0 T	FSL	TBSS	4	$P_{uncor} < 0.001$	4/1/1
Bessette *et al*[17], 2014	31	31	17.10 ± 1.88	17.00 ± 2.40	7/24	12/19	Siemens Allegra MRI 3.0 T	FSL	TBSS	56	TFCE $P < 0.05$	4/1/1
Jiang *et al*[18], 2015	35	34	29.54 ± 8.57	31.91 ± 8.80	17/18	17/17	GE Milwaukee WI 3.0 T	FSL	DTI	10	$P_{uncor} < 0.001$	4/1/1
Xiao *et al*[19], 2015	22	22	20.14 ± 1.64	20.77 ± 1.41	12/10	12/10	Siemens Magnetom Symphon 1.5 T	FSL	TBSS	10	$P < 0.01$	4/1/1
Geng *et al*[20], 2016	26	31	15.60 ± 1.27	15.60 ± 1.38	7/19	14/17	GE Signa HDX 3.0 T	PANDA software	DTI	4	AlphaSim, $P < 0.05$	4/1/1
Tatham *et al*[21], 2016	55	18	36.40 ± 10.50	33.20 ± 10.20	NA	NA	GE Signa HDX 3.0 T	FSL	TBSS	3	FEW, $P < 0.05$	4/1/1
Chang *et al*[22], 2018	108	156	20.61 ± 4.91	22.25 ± 4.35	38/93	63/45	GE Signa HDX 3.0 T	SPM8	DTI/GMV	5 & 17	$P < 0.01$	4/1/1
Wu *et al*[23], 2018	23	17	19.44 ± 4.61	18.07 ± 3.85	NA	NA	GE Signa HDX 3.0 T	PANDA	DTI	6	$P < 0.05$	4/1/1
Wei *et al*[24], 2020	49	49	30.03 ± 0.91	31.12 ± 9.95	11/38	18/31	GE Signa HDX 3.0 T	SPM8	DTI	6	GRF, $P < 0.001$	4/1/1
Wang *et al*[25], 2020	18	18	15.77 ± 1.18	16.18 ± 0.95	10/8	10/8	Siemens Trio Tim 3.0 T	NIT	FOCA	3	FDR, $P < 0.05$	4/1/1
Lee *et al*[26], 2021	19	22	15.03 ± 1.45	15.96 ± 1.02	NA	NA	Siemens Trio Tim 3.0 T	FSL	TBSS	4	FWE, $P < 0.05$	4/1/1
Roelofs *et al*[27], 2022	22	21	15.93 ± 1.45	15.09 ± 1.80	2/20	4/17	Philips Achieva 3.0 T	FSL	TBSS	2	FWE, $P < 0.05$	4/1/1
Ding *et al*[28], 2010	18	18	15.78 ± 1.20	16.20 ± 0.90	10/8	10/8	Siemens Trio Tim 3.0 T	SPM5	GMV	11	$P < 0.05$	4/1/1
Shad *et al*[29], 2012	22	22	16.00 ± 2.10	15.00 ± 2.10	10/12	11/11	GE Milwaukee WI 1.5 T	SPM5	GMV	25	FWE, $P < 0.05$	4/1/1
Vulser *et al*[30], 2015	119	461	14.45 ± 0.36	14.40 ± 0.41	41/78	158/303	NA	SPM8	GMV	8	FWE, $P < 0.05$	4/1/1
Straub *et al*[31], 2019	60	43	17.30 ± 3.44	17.62 ± 3.85	12/48	5/38	Siemens Allegra 3.0 T	SPM 12	GMV	4	FWE, $P < 0.05$	4/1/1
Chen *et al*[32], 2023	95	78	18.14 ± 4.47	17.85 ± 4.30	95/0	38/40	GE 750 1.5 T	SPM12	GMV	6	GRF, $P < 0.05$	4/1/1
Vulser *et al*[33], 2023	265	128	14.41 ± 0.52	14.40 ± 0.43	NA	NA	Siemens Corp 3.0 T	SPM 12	GMV	4	FWE, $P < 0.05$	4/1/1
Deng *et al*[34], 2023	31	29	NA	NA	8/23	11/18	GE Brivo MR355 1.5 T	SPM8	GMV	4	FWE, $P < 0.05$	4/1/1
Kang *et al*[35], 2023	54	167	35.69 ± 13.47	35.82 ± 12.91	21/33	67/100	Siemens Trio Tim 3.0 T	SPM 12	GMV	18	$P_{uncor} < 0.001$	4/1/1

DTI: Diffusion tensor imaging; FOCA: Four-dimensional (spatiotemporal) consistency of local neural activities; GMV: Gray matter volume; HCs: Healthy controls; M/F: Male or female; MRI: Magnetic resonance imaging; NA: Not available; TBSS: Tract-based spatial statistics.

NOS has three levels and a total of eight items: (1) Four items for subject selection; (2) one item for comparability between groups; and (3) three items for outcome measurement. The total score is 9 points. A result ≥ 5 points was included in the data analysis. Each study was independently reviewed and rated by two authors (H YZ and ZQ). If disagreements occurred, the papers were discussed by the authors' group to determine a consensus score.

ALE analysis

The ALE meta-analysis method was conducted by using GingerALE 3.0.2 software (www.brainmap.org/ale)[41]. ALE models each alteration focus as the center of a spherical Gaussian probability distribution. This approach is used to create spatial probability maps that highlight consistent brain region involvement in certain tasks or conditions[42]. For the ALE meta-analysis, our study was conducted in the MNI standard space. Hence, it was essential to utilize the Lancaster transformation within GingerALE 3.0.2 to convert the three-dimensional coordinates of brain regions in the Talairach space to the MNI space.

Subsequently, Gaussian function smoothing with a full width at half maximum (FWHM) was performed based on the sample size of each test group. Using the FWHM values, Gaussian functions were simulated on the three-dimensional brain mask of coordinates for a set of aberrantly activated brain regions that were reported in the study group. This process yielded three-dimensional modeling activation (MA) maps for each study group.

Afterwards, based on three-dimensional (3D)-MA maps, a 3D ALE map was generated of the Gaussian probability distribution of the activated brain regions between different study groups, and the *P* value of the activation probability of the brain regions was calculated according to the Gaussian model to construct a 3D-*P* value distribution map. Moreover, the statistical test threshold was set by a 3D-*P* value distribution plot. The main parameters were as follows: the cluster-level familywise error (FWE) correction was set at $P < 0.05$, the threshold permutations were set at $P < 0.001$ with 1000 permutations, and finally, a threshold map (ALE image) was obtained. Finally, our study used Mango software (http://rii.uthscsa.edu/mango/) to check and analyze the resulting ALE images.

Sensitivity analysis

The jackknife sensitivity analysis method was employed to assess the reproducibility of the meta-analysis outcomes. In this approach, a single study was systematically excluded from the dataset, followed by ALE meta-analysis of the remaining study data using GingerALE 3.0.2 software. This procedure was repeated 14 times (each time removing one study) to verify the consistency of the results after the exclusion of a study and to compare these results with the original analysis.

RESULTS

General information of the included studies

The systematic search generated 252 related articles, 22 of which[14-35] were ultimately selected for inclusion in this meta-analysis (Figure 1). These included 14 studies utilizing DTI and 8 utilizing VBM. Notably, the study by Chang *et al*

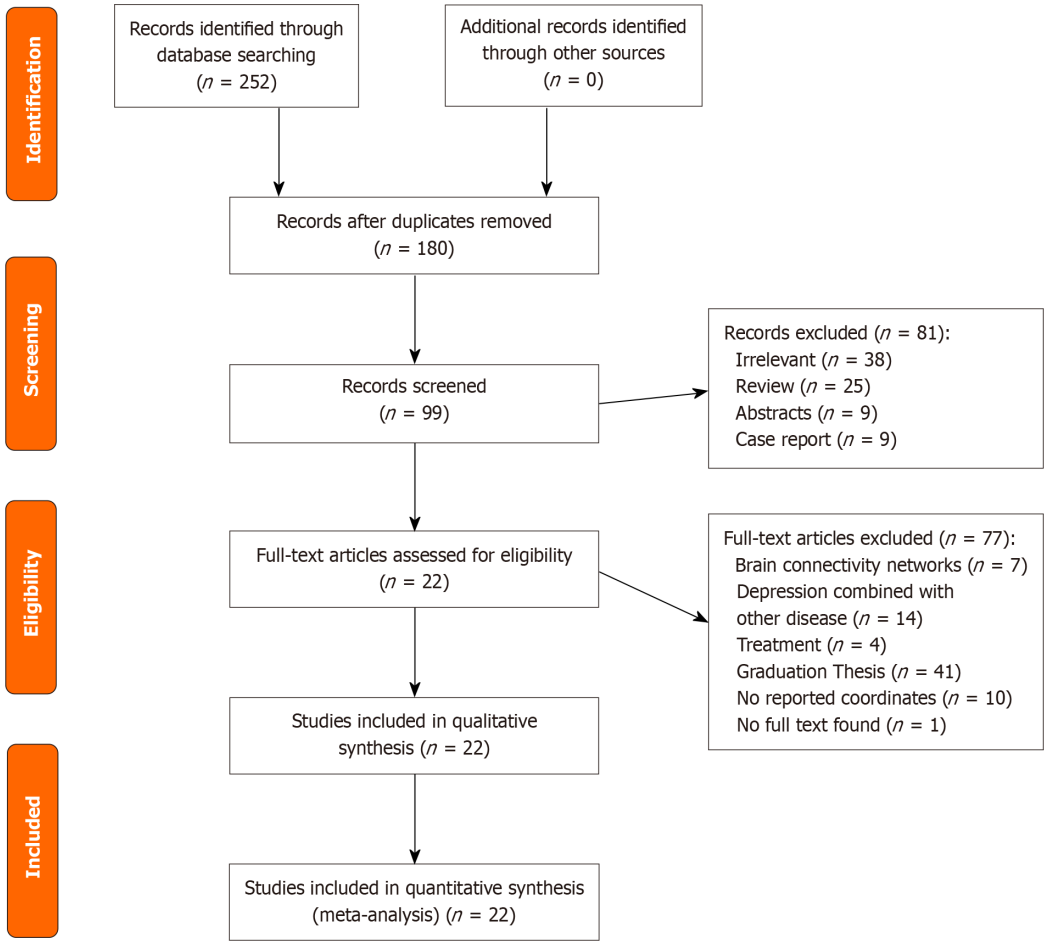

Figure 1 PRISMA flow diagram for included studies in the current meta-analysis.

[22] encompassed analyses using both DTI and VBM methodologies, thereby contributing to a total of nine VBM-based investigations. Finally, the DTI studies included 451 individuals diagnosed with MDD and 465 HCs, with the identification of alterations in 137 distinct brain areas. The VBM studies included 664 individuals diagnosed with MDD and 946 HCs and identified alterations in 80 distinct brain areas (Table 1).

The main results of changes in brain structure during adolescent and young adult MDD

ALE analysis based on DTI structural data demonstrated significant reductions in fractional anisotropy (FA) values in the right caudate head, right insula, and right lentiform nucleus putamen in adolescents and young adults with depression in comparison to HCs (Figure 2 and Table 2). However, no brain regions where FA values increased were identified. In contrast, ALE analysis based on VBM structural data did not reveal any significant changes in gray matter volume.

Sensitivity analysis

The outcomes of the sensitivity analysis demonstrated reproducibility in the findings, with the right caudate head, right insula, and right lentiform nucleus putamen showing consistent alterations in 11 of 14 analyses, 10 of 14 analyses, and 11 of 14 analyses, respectively (Table 3).

DISCUSSION

To the best of our knowledge, this meta-analysis represents the inaugural exploration of multimodal brain structural abnormalities in adolescents and young adults with depression by employing the ALE methodology, with the utilization of both DTI and VBM. The findings of this meta-analysis underscore the nuanced neurobiological underpinnings of MDD among adolescents and young adults, thus revealing significant alterations in brain structure and function. The observed reductions in FA within specific brain regions, such as the right caudate head, right insula, and right lentiform nucleus putamen, align with literature suggesting the pivotal role that these areas play in emotional regulation, cognitive processing, and the reward system[43,44]. Notably, no regions exhibited augmented FA values, thus suggesting a pervasive trend toward decreased white matter integrity across the affected neural domains. Alterations in white matter microstructure, particularly in the uncinate fasciculus, are associated with emotional dysregulation[45]. Additionally, a

Table 2 Decreased fractional anisotropy values in brain regions of adolescents and young adults with major depressive disorder

Research methods	Anatomical label	Peak MNI coordinate			ALE value	Volume in mm^3
		X	Y	Z		
FA decrease	Right caudate head	24	28	-4	0.015717618	1096
	Right insula	32	26	-8	0.012060626	656
	Right lentiform nucleus putamen	24	24	-12	0.010999768	696

ALE: Activation likelihood estimation; FA: Fractional anisotropy; MDD: Major depressive disorder; MNI: Montreal Neurological Institute.

Table 3 Jackknife sensitivity analyses

Discarded article	Right caudate head	Right insula	Right lentiform nucleus putamen
Cullen *et al*[14], 2010	N	N	N
Liu *et al*[15], 2010	Y	Y	Y
Henderson *et al*[16], 2013	Y	Y	Y
Bessette *et al*[17], 2014	N	N	N
Jiang *et al*[18], 2015	Y	Y	Y
Xiao *et al*[19], 2015	Y	Y	Y
Geng *et al*[20], 2016	Y	N	Y
Tatham *et al*[21], 2016	Y	Y	Y
Chang *et al*[22], 2018	Y	Y	Y
Wu *et al*[23], 2018	N	N	N
Wei *et al*[24], 2020	Y	Y	Y
Wang *et al*[25], 2020	Y	Y	Y
Lee *et al*[26], 2021	Y	Y	Y
Roelofs *et al*[27], 2022	Y	Y	Y

N: No; Y: Yes.

study on sex incongruence revealed lower FA in the inferior fronto-occipital fasciculus, thus emphasizing the role of white matter organization in sex identity[46]. Furthermore, findings in adolescents at high risk for bipolar disorder (BD) suggest decreased FA in various brain areas, thus emphasizing the potential role of FA as an endophenotype for BD[47]. The insula, which is a component of the limbic system, plays a pivotal role in memory and emotion processing[48]. The lack of areas showing increased FA values further emphasizes the potential of these structural changes as being neural markers of MDD, thus being potentially indicative of disrupted white matter integrity and altered neural connectivity.

However, contrary to the alterations observed in white matter through DTI analysis, this study did not identify any regions exhibiting significant changes in gray matter volume among adolescents and young adults with depression. This indicates a more consistent pattern of brain structural changes characterized by reduced integrity, particularly in regions such as the right caudate head, right insula, and right lentiform nucleus putamen, compared to HCs. The absence of significant gray matter volume changes further underscores the potential of these structural alterations as being neurobiomarkers for MDD, thus being potentially indicative of impaired white matter integrity and altered neural connectivity. These findings provide objective neuroimaging evidence, which enriches our understanding of the neurobiological mechanisms underlying depression in adolescents and young adults.

Role of the striatum in adolescent and young adult MDD patients

The putamen and globus pallidus together form the lentiform nucleus, which, along with the caudate nucleus, constitutes the striatum. The striatum, which is a subcortical structure, is divided into the ventral and dorsal striatum. The dorsal striatum includes the caudate nucleus and putamen, whereas the ventral striatum comprises the nucleus accumbens[49]. The caudate nucleus is believed to control cognitive aspects within the striatum, thus playing a role in emotional processing, motor control, and particularly in regulating cognitive functions[50,51]. The putamen, which is a critical component of the basal ganglia, is involved in learning, controlling bodily movements, and processing visual information and is associated with emotional processing, cognitive processes, motivation, and motor regulation, thus playing a key

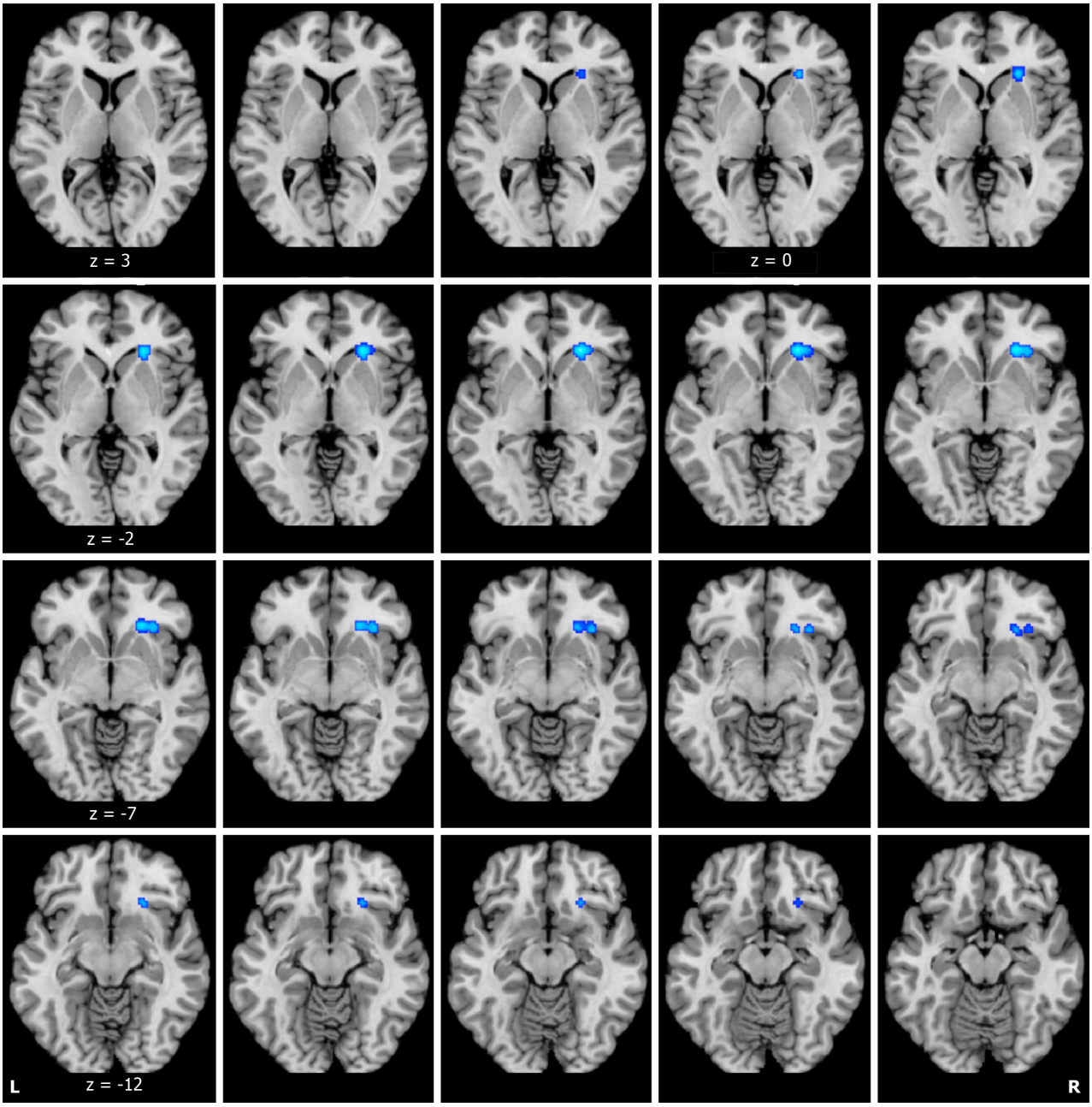

Figure 2 Brain structure alterations in adolescents and young adults with major depressive disorder compared to healthy controls.

role in action selection[52,53].

Recent research has elucidated the structural abnormalities within the striatum in MDD patients, particularly in adolescents and young adults. For instance, studies have reported of lower FA values in the right caudate nucleus among MDD patients than among HCs, thus highlighting white matter integrity impairment[54]. Furthermore, Ding *et al*[55] reported that individuals with MDD exhibit reduced FA values across the striatum bilaterally, thus suggesting widespread structural changes within this brain region. Moreover, volumetric studies have noted a reduction in the size of the striatum among MDD patients, with one study demonstrating volume reductions in the ventral striatum and putamen even before the onset of the disorder in adolescents at risk due to parental MDD history[56,57]. This familial predisposition is further evidenced by findings of increased right striatum gray matter volume among first-degree relatives of MDD patients, thus suggesting that striatal structural abnormalities may be a risk factor for developing MDD [58].

These findings, although predominantly cross-sectional, provide a foundational basis for future longitudinal studies aimed at elucidating the causal relationships between striatal volume abnormalities and the progression of MDD. The consistent observation of striatal volume reductions in MDD patients compared to HCs across various studies underlines the potential of the striatum as being a key neural substrate in the pathophysiology of depression.

Role of the insula in adolescent and young adult MDD patients

This meta-analysis demonstrated a decrease in FA values within the right insula among adolescents and young adults

with MDD. The insula, which is a cortical structure with extensive connections to various cortical and limbic regions, plays a critical role in diverse cognitive, emotional, and regulatory functions, including interoceptive awareness, emotional responses, and empathic processes[59]. Several meta-analyses based on structural MRI studies have reported of bilateral reductions in insular gray matter volume in individuals with MDD[60,61]. Lu *et al*[62] observed a decrease in the gray matter volume of the right insula with the progression of MDD. Furthermore, functional MRI studies have identified alterations in functional connectivity within significant networks centered on the insula, such as the salience network, default mode network (DMN), and central executive network (CEN), in MDD patients[63,64]. The insula's mediation of dynamic switches between the DMN and CEN facilitates the allocation of cognitive resources, such as attention and working memory. Hence, alterations in the connectivity strength within these networks in affective disorders can lead to cognitive impairments[65].

Task-based functional MRI studies have demonstrated atypical insula activity during executive function and emotional processing tasks in individuals with MDD, thus potentially revealing the difficulties in cognitive-emotional integration observed in individuals with adolescent depression[66]. Positron emission tomography studies, such as those conducted by Delaveau *et al*[67], have also noted reduced insula activation in MDD patients. Moreover, changes in insula activity have been observed following various MDD treatments, including pharmacotherapy, deep brain stimulation, and cognitive behavioral therapy, which suggests that the region has a broader role in mediating antidepressant responses and remission[68].

Collectively, these findings, which are derived from diverse neuroimaging methodologies, consistently underscore the critical role of the insula in the neuropathology of depression[69]. These findings further highlight functional and structural abnormalities in the insula as being key neurobiological features of affective disorders.

Reason for the lack of positive findings in the VBM data in this meta-analysis

This meta-analysis did not identify changes in gray matter volume in the brains of adolescents or young adults with depression, which may be attributed to the relatively small number of reported brain regions with altered gray matter volume in the included studies. Among the eight studies that were analyzed, all of them reported regions of reduced gray matter volume, yet five of these studies had fewer than ten central coordinates for the reported areas of abnormal activity. The ALE meta-analysis, which functions as a probability distribution, is more influenced by studies reporting of a greater number of activation points. The scarcity of coordinates may fail to meet the threshold criteria, or the spatial information of these activity regions may be too dispersed to allow for the consolidation of results in areas proximal to the activation points. This dispersion could also explain the absence of increased activity findings in the DTI-based meta-analysis[70]. Therefore, whether there are specific brain regions in adolescents and young adults with depression that exhibit reduced gray matter volume relative to HCs and whether isolated DTI meta-analyses can demonstrate regions of increased activity warrant further exploration.

Limitations

First, the adoption of stringent exclusion criteria, particularly the exclusion of studies involving pharmacological or acupuncture treatments, has resulted in a smaller amount of literature for analysis. Second, although the ALE methodology effectively mitigates the risk of false-positives, it is less adept at circumventing false-negatives, thus posing a challenge to the robustness of the findings. Last, the number of studies employing VBM was limited to nine, thus culminating in a smaller aggregate of differential brain regions, which did not yield results of significant increases or decreases. However, ALE meta-analysis for brain imaging has the advantage of integrating locational information across diverse studies, thus offering a promising avenue for future explorations into consistent brain activity changes in specific disorders.

CONCLUSION

In conclusion, the structural alterations observed in the striatum and insula among adolescents and young adults with MDD may be indicative of the recurrent nature of the disorder. These findings underscore the potential of these structural changes as being neural markers for MDD, thus offering insights into the neuropathology of this disorder. Future research should aim to elucidate the longitudinal implications of these structural alterations.

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FOOTNOTES

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designation as co-corresponding authors underscores our shared responsibilities in handling correspondence, communicating with peers, and providing essential guidance throughout the research process.

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Research fronts and researchers of *World Journal of Psychiatry* in 2023: A visualization and analysis of mapping knowledge domains

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Abstract

BACKGROUND

In the rapidly evolving landscape of psychiatric research, 2023 marked another year of significant progress globally, with the *World Journal of Psychiatry* (*WJP*) experiencing notable expansion and influence.

AIM

To conduct a comprehensive visualization and analysis of the articles published in the *WJP* throughout 2023. By delving into these publications, the aim is to determine the valuable insights that can illuminate pathways for future research endeavors in the field of psychiatry.

METHODS

A selection process led to the inclusion of 107 papers from the *WJP* published in 2023, forming the dataset for the analysis. Employing advanced visualization techniques, this study mapped the knowledge domains represented in these papers.

RESULTS

The findings revealed a prevalent focus on key topics such as depression, mental health, anxiety, schizophrenia, and the impact of coronavirus disease 2019. Additionally, through keyword clustering, it became evident that these papers were predominantly focused on exploring mental health disorders, depression, anxiety, schizophrenia, and related factors. Noteworthy contributions hailed authors in regions such as China, the United Kingdom, United States, and Turkey. Particularly, the paper garnered the highest number of citations, while the American Psychiatric Association was the most cited reference.

CONCLUSION

It is recommended that the *WJP* continue in its efforts to enhance the quality of papers published in the field of psychiatry. Additionally, there is a pressing need to delve into the potential applications of digital interventions and artificial

intelligence within the discipline.

Key Words: *World Journal of Psychiatry*; Psychiatry; Mapping knowledge domains; Visualization; Analysis

Core Tip: In 2023, the papers in the journal *World Journal of Psychiatry* predominantly centered around four key areas: Mental health, depression and anxiety, schizophrenia, and related factors. Moreover, a substantial number of papers originated from authors based in countries such as China, United Kingdom, United States, and Turkey. In terms of citation frequency, the study emerged as the most cited paper, indicating its significant impact within the field. In addition, the American Psychiatric Association was the most frequently referenced source among the cited literature in published papers.

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INTRODUCTION

Currently, psychiatric research is undergoing a phase of dynamic transformation driven by the relentless progression of science and technology and an increasing societal concern regarding mental health issues. Within this landscape, psychiatry is facing both new challenges and opportunities. Presently, psychiatric research is making strides toward a deeper comprehension of the pathogenesis and pathophysiological foundations of various mental disorders. This progress is facilitated by interdisciplinary collaboration across fields such as neuroscience, genetics, psychology, and sociology, which has significantly advanced our grasp of the biological basis of mental health conditions and the impact of environmental factors. Advancements in neuroscience have provided invaluable insights into the intricate relationship between brain structure and function, shedding light on the neurobiological mechanisms that underlie mental disorders. This integration of modern has bridged the interest of neurology and psychiatry, further enriching our understanding of psychiatric conditions[1]. Moreover, genetic research has played a crucial role in emphasizing the significance of genetic factors in mental disorders development. In studies in imaging genetics and genomics, researchers are beginning to unravel the molecular and genetic architecture of neural phenotypes, offering insights into the neural mechanisms involved in the manifestation of genetic risks for psychopathology[2]. Additionally, contributions from psychology and sociology are substantial, as they provide valuable perspectives on individual behavioral patterns, social interactions, and environmental influences on mental health. By integrating insights from these disciplines, we can attain a more comprehensive understanding of the complexities surrounding the development and treatment of mental illness.

Furthermore, psychiatric research is progressively transitioning towards individualized and precision medicine, aiming to tailor treatments to the unique needs of each patient. This paradigm shift is fueled by advancements in genomics, biomarkers, imaging technologies, and other cutting-edge tools that enable researchers to discern nuanced biological and clinical characteristics among individuals. By leveraging these technologies, researchers can develop personalized treatment plans that enhance efficacy and outcomes. For instance, advances in genomics have provided profound insights into the genetic foundations of mental illness. Genome-wide association studies have emerged as instrumental in identifying genetic risk variants associated with complex diseases, offering valuable clues for personalized intervention strategies[3]. Biomarkers, on the other hand, provide supplementary information about diseases or interventions at various stages, from pathogenesis to recovery, aiding the customization of therapeutic approaches[4]. Moreover, neuroimaging plays a pivotal role in establishing a biological basis for psychiatric diagnosis[5]. Through sophisticated imaging techniques, researchers can detect subtle changes in brain structure and function, leading to a deeper understanding of the underlying pathophysiological processes of psychiatric disorders. This insight enables the tailoring of treatment plans to align with individualized treatment plans accordingly. The shift towards individualized medicine signifies the importance of psychiatrists viewing each patient as a unique individual, departing from a one-size-fits-all approach to care[6]. Integrating precision psychiatry into personalized treatment strategies ensures that interventions are precisely tailored to the specific characteristics and needs of each patient, maximizing therapeutic efficacy[7].

Additionally, psychiatric research is actively exploring novel treatments and interventions that extend beyond traditional pharmacological and psychotherapeutic approaches. Non-pharmacological treatments, such as psychosocial interventions, cognitive training, and lifestyle modifications, are gaining traction in the field[8-10]. These approaches aim to significantly enhance individuals' mental well-being and improve their quality of life by addressing psychological, social, and lifestyle factors holistically. Concurrently, the landscape of mental healthcare is being transformed by advancements in digital healthcare technologies and artificial intelligence. Artificial intelligence applications are increasingly assisting in psychiatric diagnoses, symptom tracking, disease prognosis, and psychoeducation[11]. As society continues its digital evolution, the integration of artificial intelligence into psychiatry is poised to expand

significantly[12].

Besides, psychiatric research is actively responding to societal changes and global challenges. The coronavirus disease 2019 (COVID-19) pandemic, in particular, has emerged as a significant threat to global mental health. Within the field of psychiatry, researchers have extensively scrutinized the pandemic's impact on mental health and have endeavored to devise effective psychological interventions and support measures[13-15]. There is a growing acknowledgment that the relationship between mental health and illness is influenced not only by biological determinants but also by socio-cultural factors. Unlike disciplines such as cardiology or nephrology, psychiatric diagnosis and treatment are profoundly influenced by cultural and societal norms[16]. Attitudes and perceptions surrounding mental health issues can significantly affect individuals' willingness to seek medical help and clinicians' assessment of their condition. Therefore, psychiatric research and practice must consider the complexities of human behavior and socio-cultural contexts.

On a global scale, numerous journals are dedicated to publishing research in the field of psychiatry, with a focus on advancing psychiatric research and contributing to population health and societal development. Among these, the *World Journal of Psychiatry* (*WJP*) stands out as a high-quality, online, open-access, single-blind peer-reviewed journal published by the Baishideng Publishing Group. The paramount objective of *WJP* is to showcase and promote distinguished research in the field of psychiatry, to help advance development of this field. Articles published in *WJP* are high-quality, clinical and basic, influential research articles by established academic authors as well as new researchers. Recognizing that mapping knowledge domains serves as a powerful visualization technique capable of elucidating complex relationships such as networks, structures, interactions, and evolutions among knowledge units or clusters[17], *WJP* endeavors to explore trending topics, identify active authors, and address pressing issues in psychiatry. To achieve this objective, this study aims to utilize knowledge domain visualization techniques to analyze papers published by *WJP* in 2023. By doing so, it seeks to provide valuable references for subsequent research endeavors in psychiatry, thus contributing to the continuous development of the field.

MATERIALS AND METHODS

Data source

The study utilized the Web of Science Core Collection as the primary data source, focusing specifically on the *WJP* as the target journal. The publication period was restricted from January 1, 2023 to December 31, 2023, resulting in the identification of a total of 107 articles.

Procedure

For data analysis, COOC 14.3 software[18] was employed, and rose diagrams were generated. Additionally, co-occurrence analysis and cluster analysis were conducted using VOSviewer 1.6.20 software[19]. The downloaded data underwent comprehensive analysis, covering aspects such as keywords, authors, institutions, countries, and cited literature.

RESULTS

High-frequency keywords and keyword clustering

The study revealed high-frequency keywords and identified keyword clusters within the papers published in the *WJP* in 2023. Among the 502 keywords analyzed, 49 appeared two or more times (Figure 1), while 17 keywords appeared three or more times (Figure 2). Notably, five keywords appeared six times or more: "depression" (16), "mental health" (10), "anxiety" (7), "schizophrenia" (6), and "COVID-19" (6).

Furthermore, cluster analysis of the 49 keywords revealed their classification into four distinct groups (Figure 3). The first category encompassed terms such as mental health, digital interventions, and COVID-19. Keywords related to anxiety, depression, and quality of life were grouped in the second category. The third category comprised keywords such as schizophrenia, Chinese, and medical students. Lastly, terms like influencing factors, risk factors, and mediating effect comprised the fourth category.

Authors, institutions, and countries (regions)

The study examined the authors, institutions, and countries featured in the 2023 issue of the *WJP*. Among the 540 authors involved, 22 authors contributed to two or more papers. Notably, five authors, namely Zhou B, Zhang Y, Mei X, Zou ZL, and Liu XQ, each authored three papers. Additionally, 17 authors, including Ferber SG, contributed two papers each (Figure 4).

In terms of institutions, the analysis revealed the involvement of 199 institutions, with 23 of them publishing two or more papers. Leading the list were Fujian Medical University, Soochow University, and Hebei Medical University, each contributing five papers. Additionally, six institutions, such as the University of Southampton, published three papers each, while 14 institutions, including Columbia University, published two papers each (Figure 5). Additionally, the study covered 26 countries (regions), with 13 of them publishing two or more papers (Figure 6). Notably, China led with 80 publications (including two papers from Taiwan), followed by United States (5), United States (5), and Turkey (4).

Figure 1 Word cloud of 49 keywords. The color red indicates that the keyword occurs 6 times or fewer, blue indicates that the keyword occurs between 3 and 5 times, and green indicates that the keyword occurs twice.

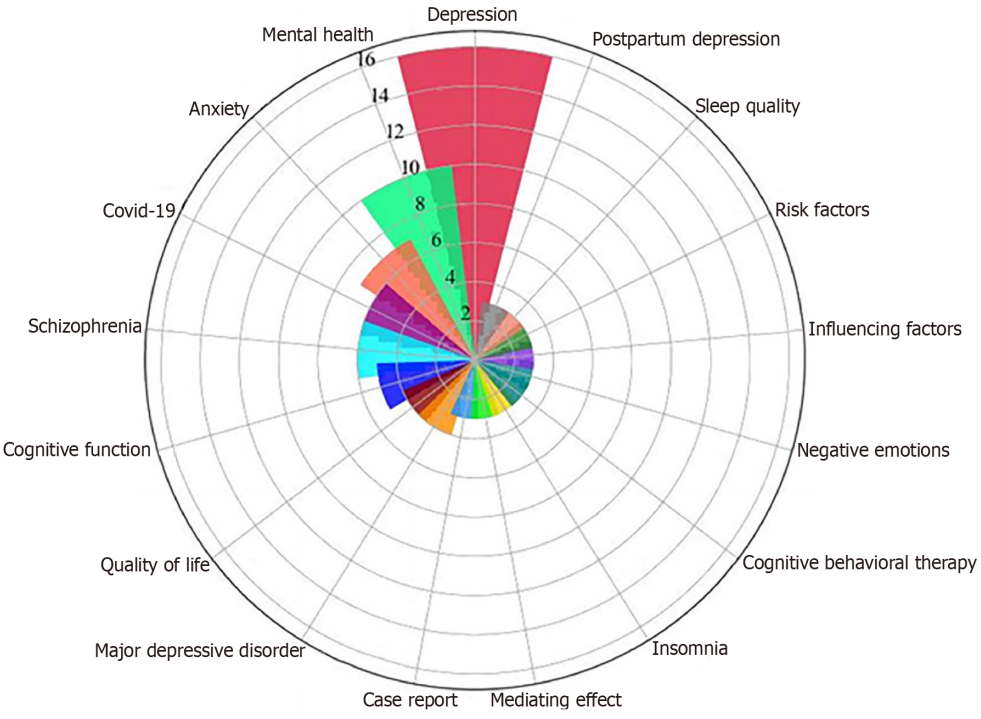

Figure 2 Seventeen high-frequency keywords. COVID-19: Coronavirus disease 2019.

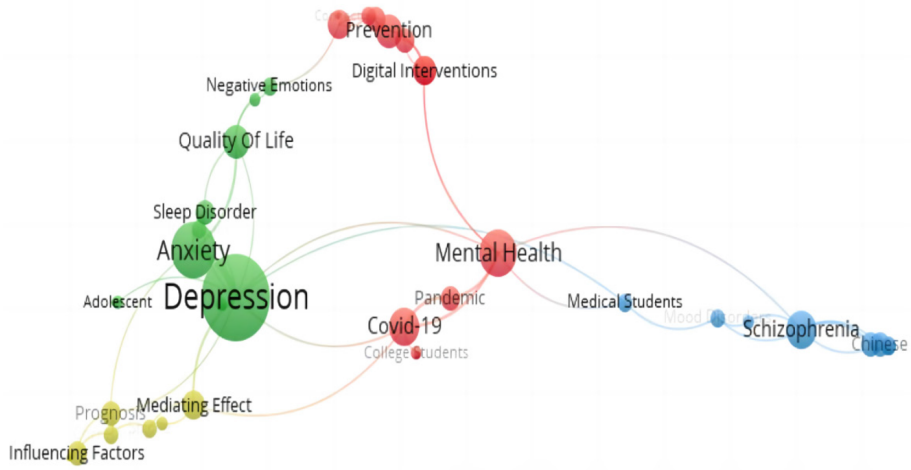

Figure 3 Cluster map of 49 keywords.

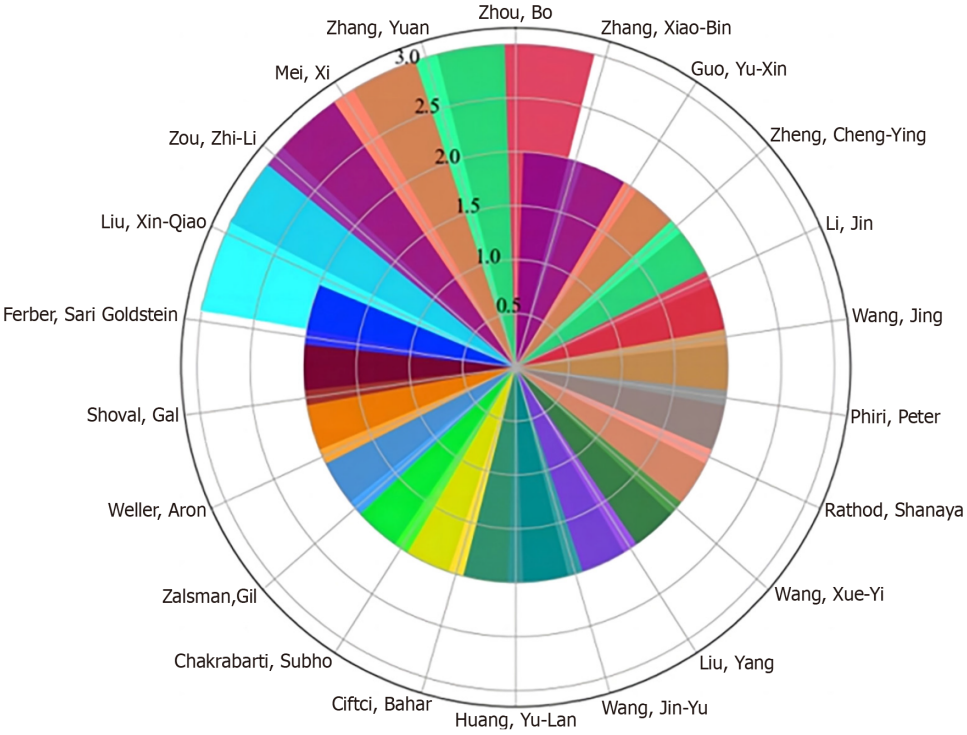

Figure 4 Authors with two or more publications.

Cited literature

The study revealed that out of the 5181 documents cited in the analyzed papers, 77 were cited two or more times. Notably, the most frequently cited literature was the American Psychiatric Association[20], referenced five times. In terms of connection strength within the co-occurrence graph of cited literature, Kotov *et al*[21] had the highest connection strength (37). This literature was frequently cited in conjunction with other works such as the American Psychiatric Association[20], Caraci *et al*[22], and others (Figure 7). As of the time of data retrieval, 22 out of the 107 papers published in 2023 had been cited one or more times. Among them, the paper titled "Delivering substance use prevention interventions for adolescents in educational settings: A scoping review" by Liu *et al*[23] garnered the highest number of citations, with a total of 10 times. The following closely followed was "Kynurenine pathway of tryptophan metabolism in pathophysiology and therapy of major depressive disorder" by Badawy *et al*[24], cited three times.

DISCUSSION

This study analyzes the papers published in *WJP* in 2023, utilizing knowledge graph visualization to explore prominent

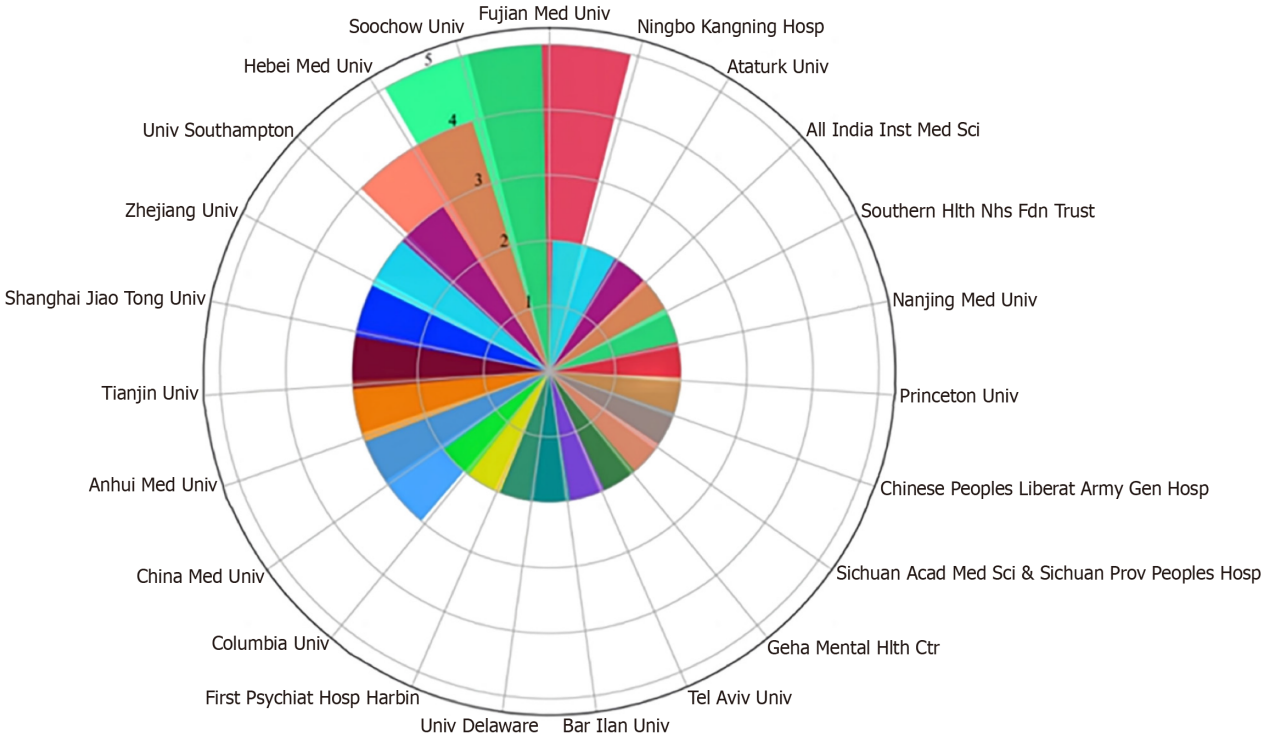

Figure 5 Institutions with two or more publications.

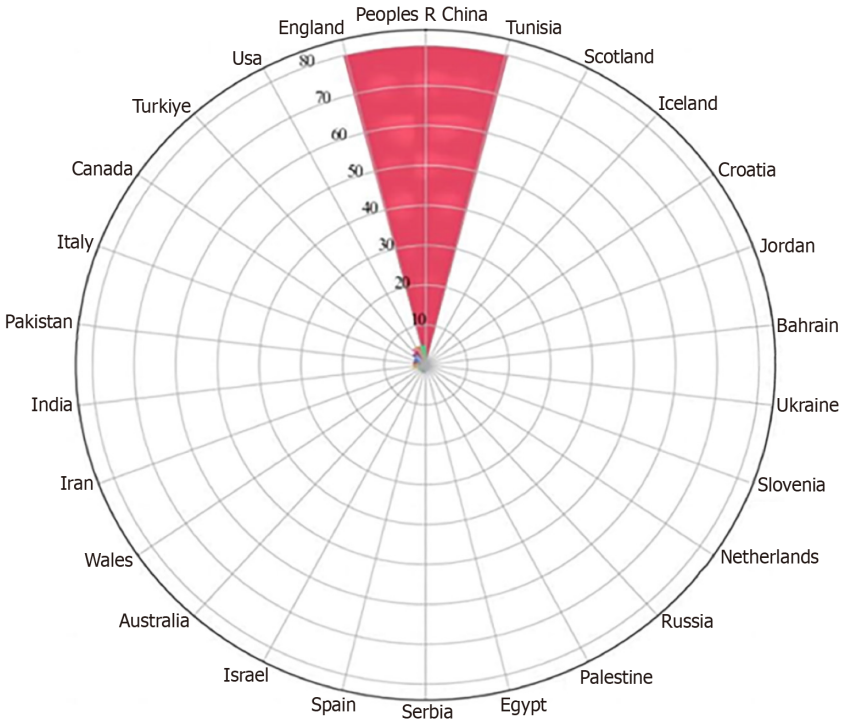

Figure 6 Countries (regions) with two or more publications.

topics, authors, institutions, and countries within the journal. Such an analysis offers valuable insights for guiding future research endeavors in the field of psychiatry. These findings contribute to the deepening of our comprehension within the field of psychiatry and further the advancement of research in this domain.

The findings of this study highlight the prevalence of keywords such as "depression", "mental health", "anxiety", "schizophrenia", and "COVID-19" within the *WJP* in 2023, underscoring their significance in psychiatric discourse. Notably, "depression" stands out as the most frequently occurring keyword, indicating its prominence in research discussion. Researchers have approached the topic of depression from various perspectives, as evidenced by multiple studies. For instance, cross-sectional surveys have explored interventions aimed at mitigating depression by reducing

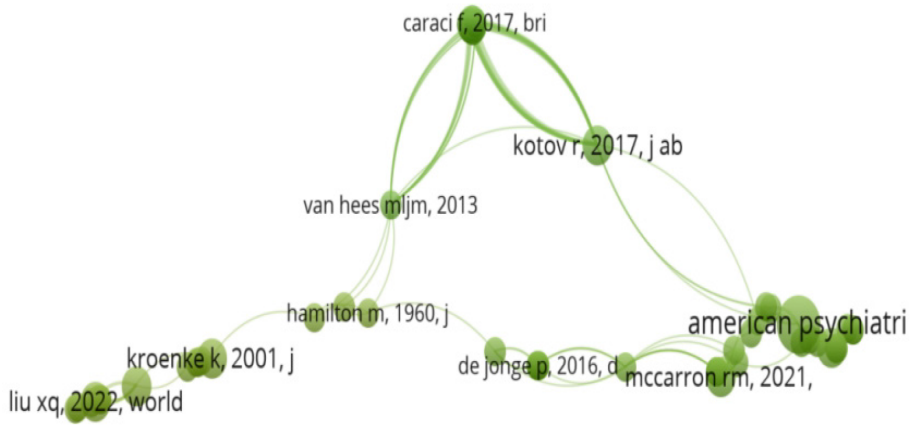

Figure 7 Co-occurrence network of references.

excessive smartphone usage and enhancing sleep quality[25]. Besides, investigations have delved into the clinical characteristics and the connection between posttraumatic stress disorder and trauma-induced depression, along with their potential treatments[26]. Additionally, studies have provided a comprehensive overview of the growth patterns, trends, and research themes concerning dialysis and depression[27].

Further investigation has revealed that the keywords found in the 2023 papers of *WJP* can be categorized into four distinct groups. In the first category, keywords such as mental health, digital interventions, and COVID-19 emerged prominently. Throughout 2023, several studies persisted in investigating mental health issues within the context of the novel coronavirus pandemic[28,29].

Mental health has always been an important area of psychiatric research[30,31]. It can be anticipated that mental health research will continue to garner attention. Category 2 encompassed keywords such as anxiety, depression, and quality of life. Notably, anxiety and depression frequently appeared together as keywords[32,33]. Keywords in category 3 comprised schizophrenia, Chinese, and medical students. Schizophrenia remained a focal point of research interest in 2023[34,35]. Lastly, category 4 included terms such as influencing factors, risk factors, and mediating effects. Papers in this category focused on elucidating various "factors"[36,37]. In addition to these categories, two papers garnered significant attention from psychiatry researchers. One of these papers, authored by the American Psychiatric Association [20], presented a diagnostic and statistical manual on mental disorders. The other paper, by Kotov *et al*[21], posited that traditional taxonomies suffer from limited reliability and validity due to arbitrary boundaries between psychopathology and normality, unclear distinctions between disorders, frequent comorbidity among disorders, inherent heterogeneity within disorders, and diagnostic instability. Consequently, the study proposed the Hierarchical Taxonomy of Psychopathology model.

This study also revealed that among the 540 authors featured in the 2023 issue of the *WJP*, five authors (Zhou B, Zhang Y, Mei X, Zou ZL, and Liu XQ) exhibited considerable activity. Notably, the most cited paper was authored by Liu *et al* [23], which, as a scoping review, delved into the types, characteristics, and effectiveness of substance use interventions in educational settings for adolescents. It is widely recognized that the involvement of prolific authors significantly bolsters the reputation and impact of a journal. When esteemed scholars opt to disseminate their research through a particular journal, it inherently attracts a broader readership and garners attention from fellow academics. Hence, journals should proactively solicit submissions from such active authors within the field to augment the competitiveness and allure of the publication.

Moreover, regarding the affiliations of authors and their respective countries (regions), the notable institutions with a higher volume of published papers include Fujian Medical University, Soochow University, and Hebei Medical University. Similarly, the countries contributing to a greater number of published papers are China, United Kingdom, and United States. In future research endeavors, it is imperative to strengthen collaborations between research institutions and foster international cooperation. Such collaborative efforts facilitate resource, data, and knowledge sharing, thereby advancing scientific progress. Moreover, these collaborations contribute to the development of more comprehensive and productive solutions for the prevention, diagnosis, and treatment of mental illnesses.

This study has a few shortcomings. Firstly, while the mapping of knowledge domains was employed in this study, only literature published in 2023 was analyzed. Future studies could consider including literature from different time periods for a more comprehensive analysis. Secondly, the primary literature selected for this study was published in the *WJP*. For future research, it is recommended to select multiple psychiatry-related journals to analyze research trends and hotspots in psychiatry from a broader perspective.

CONCLUSION

In 2023, keywords such as depression, mental health, anxiety, schizophrenia, and COVID-19 were notably prevalent in papers published in the journal *WJP*. These papers predominantly centered around four key areas: Mental health,

depression and anxiety, schizophrenia, and related factors. Moreover, a substantial number of papers originated from authors based in countries such as China, United Kingdom, United States, and Turkey. In terms of citation frequency, Liu *et al*[23] emerged as the most cited paper, indicating its significant impact within the field. In addition, the American Psychiatric Association (2013) was the most frequently referenced source among the cited literature in published papers. Moving forward, this journal must maintain its commitment to enhancing the quality of papers within the realm of psychiatry. Additionally, exploring the integration of digital interventions and artificial intelligence within the field presents promising avenues for advancing research and improving clinical outcomes.

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FOOTNOTES

Author contributions: Xie YT developed the study protocol and wrote the original draft; Yang YJ contributed to the manuscript development. All authors reviewed and approved the final manuscript.

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Emerging global interest: Unraveling the link between diabetes mellitus and depression

Samah W Al-Jabi

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Abstract

BACKGROUND

Studies have shown a strong bidirectional association between diabetes and depression, with diabetes increasing the risk of developing depression and vice versa. Depression among patients with diabetes is associated with poor glycemic control, complications, and poor self-care.

AIM

To explore the present state of research globally concerning diabetes and depression, to aid understanding the current research landscape and identify potential future areas of research.

METHODS

A bibliometric approach was used, utilizing the Scopus database to gather pertinent research articles released from 2004 to 2023. Analyses encompassed publication patterns, significant contributors, research focal points, prevalent themes, and the most influential articles, aimed at discerning emerging research subjects.

RESULTS

A total of 3229 publications that met the search criteria were identified. A significant increase in the number of publications related to diabetes and depression has been observed in the past two decades. The most productive nation was the USA (n = 1015; 31.43%), followed by China (n = 325; 10.07%), the UK (n = 236; 7.31%), and Germany (n = 218; 6.75%). Three principal themes in research on depression and diabetes were delineated by the analysis. First, the exploration of the elevated prevalence and etiology of this comorbidity; second, the focus on interventions, particularly randomized controlled trials, aimed at enhancing diabetes management among individuals with depression; and finally, the investigation of the involved risk factors and biological mechanisms underlying this bidirectional relationship.

CONCLUSION
There has been a recent surge of interest in the relationship between diabetes and depression. This could aid researchers to identify areas lacking in the literature and shape future research.

Key Words: Diabetes mellitus; Depression; Bibliometric; Visualization; Global

Core Tip: Although there have been numerous studies examining research productivity in diabetes or depression separately, there is a notable absence of a bibliometric analysis concentrating on the intersection of both conditions. Conducting bibliometrics in this regard will enable us to pinpoint the primary countries, institutions, journals, and research themes involved. Such insights will provide more comprehensive understanding of the present research landscape and offer guidance for future inquiries. By analyzing publication patterns across time, we can anticipate burgeoning areas of interest, thereby aiding in research funding allocations, program formulation, and policy development.

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INTRODUCTION

Depression and diabetes mellitus (DM) have a complicated link in which one can both cause and predispose patients to the other[1-3]. Studies point to a strong correlation[4,5] between the incidence of diabetes and depression, especially type 2 DM (T2DM). However, the two diseases are negatively correlated. Individuals with severe depression may suffer from diabetes three times more frequently than the general population[6]. Common molecular pathways involving inflammation, autonomic dysfunction, changes to the central nervous system, and hypothalamic–pituitary–adrenal (HPA) axis activation are linked to these disorders[1,5,7,8].

T2DM and depression are inversely related to biological processes, including low-grade inflammation, hyperglycemia, and (micro)vascular dysfunction[8]. Depression and T2DM are related to molecular changes that impact the sympathetic nervous system, the HPA axis, and subclinical inflammation[2].

Patients with diabetes who have comorbid depression are more likely to have poor glycemic control, to use healthcare more frequently, to have more complications, and to die[3]. Patients with T2DM who have poor glycemic control are at risk of experiencing more complications from their disease and becoming depressed[9]. An emotional state brought on by having diabetes and the responsibility of self-management, diabetes distress, on its own, raises complications associated with the disease and is associated with worse health outcomes[6].

Depression and anxiety may arise from the psychological burden of diabetes and from the detrimental effects of problems on quality of life[1,5]. T2DM, depression, and anxiety are complexly related to psychosocial factors, including stress, lifestyle, socioeconomic background, and genetic background[1,5].

In individuals with diabetes, both pharmacological and individual psychological depression therapies are effective; however, the current treatment options are limited and have conflicting effects on glycemic outcomes[1,7]. Improving outcomes associated with diabetes appears to be best achieved by collaborative care programs that simultaneously manage both conditions[3]. It is advised to routinely screen diabetic patients for depression and distress, and psychological therapies tailored to diabetes may help depressed patients better manage their condition[6,10].

While research on diabetes and depression is growing, a gap exists in the bibliometric analysis of this specific link. This comprehensive approach to publication patterns can reveal key trends, influential institutions, and impactful research areas[11,12]. Bibliometrics helps us understand where the field stands and what future directions hold. In contrast, systematic reviews summarize existing research[13,14]. Notably, despite numerous studies on research productivity in either diabetes[15-23] or depression[24-31], a bibliometric analysis focusing on the co-occurrence of both conditions is lacking.

Bibliometrics in this context would allow us to identify leading countries, institutions, journals, and research themes. This knowledge will provide a deeper understanding of the current research landscape and guide future investigations. By analyzing publication trends over time, we can predict emerging areas of interest and inform research funding decisions, and program and policy development.

MATERIALS AND METHODS

Data sources

The research draws upon data retrieved from the Scopus database, which offers distinct advantages over other databases [32-35]. First, Scopus provides broad global and regional coverage of scientific journals, conference proceedings, and books, ensuring the inclusion of high-quality data. Second, Scopus furnishes comprehensive author and institution profiles through advanced profiling algorithms and manual curation, ensuring accuracy and completeness. Third, Scopus serves as a vital bibliometric data source for various large-scale analyses in research evaluations, scientific landscape studies, policy assessments, and university rankings. Fourth, Scopus data are accessible for specific academic research endeavors, facilitating investigations into areas such as researcher mobility, network visualizations, and spatial bibliometrics. Finally, Scopus offers individual profiles for authors, institutions, and publications, making it highly user-friendly for practical applications.

Search strategy

A literature search on depression and DM was conducted on April 13, 2024. The Scopus online advanced search function was utilized to identify relevant studies published between January 2004 and December 2023. Synonyms for both DM and depression were included in the search strategy.

Step 1: Several previous systematic reviews and meta-analyses on DM were consulted to identify relevant search terms [36-43]. These terms were subsequently incorporated into the article title. The title included: diabetic, diabetes, type 2 DM, type 1 DM, T2DM, T1DM, glycemic control, glycaemic control, elevated blood glucose, and elevated blood sugar.

Step 2: The first step involved narrowing the publications to only those containing the terms "depression and linked terms" in their titles. To accomplish this, we utilized several previous systematic reviews and meta-analyses on DM[36-43] to generate keywords, which were then used in the Scopus search engine to fulfill the study objective. The "Article Title" field was populated with the following terms: Depress* OR "seasonal affective" OR dysthym* OR "affective disorder" OR "mood disorder*" OR "bipolar disorder".

To avoid any misinterpretation, we excluded publications related to depressed heart disease or depressed cardiac disease. Consequently, keywords were used instead of conducting a title/abstract search. The title search yielded a minimal number of false-positive results, rendering it a dependable approach[44-46]. Conversely, a title/abstract search may generate numerous false positives, focusing not primarily on DM and depression but on other subjects.

Step 3: The research limits its scope to peer-reviewed scientific journal articles, excluding books, book chapters, retracted articles, and errata.

Bibliometric analysis

The current research environment was mapped using numerical data from the collected articles. This analysis focused on publication trends, the types of documents included, where they were published (journals), and who produced them (countries, institutions, and funding agencies). Additionally, consideration was given to how often the articles were cited by others to measure their influence.

Visualization analysis

The search approach was utilized, and the collected data were exported to a "CSV" file format in Microsoft Excel. VOSviewer 1.6.20 (Leiden University, Leiden, The Netherlands) was used to illustrate the network characteristics among countries and co-occurring terms found in titles and abstracts, providing a visual representation of the results[47,48]. VOSviewer can be used to construct knowledge networks rooted in scientific principles, illustrating the evolution of research fields and facilitating the anticipation of future research trends and international collaborations. The co-occurrence analysis of VOSviewer categorizes terms into distinct clusters, each represented by a unique color. Through a term co-occurrence network, maps were generated to identify the most frequently occurring terms in titles and abstracts, thereby delineating research hotspots as thematic clusters.

Statistical analysis

After being exported from Scopus, the data were imported into Microsoft Word from Microsoft Office Excel. VOSviewer version 1.6.20 and Microsoft Excel 2013 were used to create the figures. Frequencies and percentages were used to present descriptive statistics. The top 10 rankings in each category were taken into consideration after bibliometric analysis was transformed into rankings incorporating countries, cited publications, funding agencies, journals, and institutions. A space was added between ranking numbers when bibliometric analysis produced the same ranking number.

RESULTS

Evolution and growth of publications

Between 2004 and 2023, 3229 publications that met the search criteria were identified. Of these, 2711 (83.96%) were original research articles, 286 (8.86%) reviews, 90 (2.79%) letters to the editor, and 142 (4.40%) were categorized under other classifications, such as notes or editorials. Over the past decade, there has been a notable surge in publications

concerning the correlation between DM and depression. In 2004, there were 45 articles published on this topic, which escalated to 268 by 2023. Particularly since 2010, the rate of publication growth has accelerated significantly, with an average of over 195 articles being published each year (Figure 1). Linear regression analysis confirmed this pattern, revealing a modest positive correlation (R^2 = 0.8823, P < 0.001) between the yearly count of publications and their respective publication years.

Top active countries

Scientific research on DM and depression has involved the participation of 160 countries. The top 10 countries in this research generated a combined total of 2249 publications, constituting 69.65% of all analyzed publications (Table 1). The findings showed that the USA (n = 1015; 31.43%) was the most productive nation, followed by China (n = 325; 10.07%), the UK (n = 236; 7.31%), and Germany (n = 218; 6.75%). Figure 2 illustrates a network visualization map that depicts research collaborations among 24 countries, each contributing a minimum of 30 articles. The size of the nodes and the thickness of the connecting lines signify the extent of cross-country collaboration, with the USA demonstrating the most robust collaboration.

Contributed institutions

Table 2 presents a comprehensive compilation of the top 10 most productive institutions engaged in research on DM and depression from 2004 to 2023. These distinguished academic and research entities collectively made significant contributions, constituting 12.54% of the total number of published articles (n = 405) within this domain. The University of Washington in the USA showcased its prominence as the foremost contributor, generating 87 articles (2.69%). Tilburg University in Netherlands contributed 63 articles (1.95%), while McGill University in Canada produced 54 articles (1.67%). Notably, the USA had four listed institutions, the Netherlands three, Canada two, and the UK one institution among the top-ranked contributors.

Top 10 funding agencies

A total of 1302 publications, representing 40.32% of the retrieved articles, received financial support. Table 3 lists the top 10 funding agencies associated with publications relevant to DM and depression. These agencies contributed 20.04% (n = 647) of the articles. The National Institute of Diabetes and Digestive and Kidney Diseases in the United States (n = 189; 5.85%) emerged as the foremost funding source, followed by the National Institutes of Health in the USA (n = 153; 4.74%) and the National Institute of Mental Health in the USA (n = 125; 3.87%). The USA featured prominently with five funding agencies on the list, while China, Canada, Germany, Australia, and Brazil each had one agency represented in this list.

Active journals

The top 10 most active journals together published 595 articles related to DM and depression, constituting 18.43% of all publications (Table 4). *Diabetes Care* emerged as the primary contributor, publishing the greatest number of papers (n = 139), accounting for 4.30% of the total publications. Similarly, *Diabetic Medicine* secured the second position with 96 papers (2.97%), followed by the *Journal of Affective Disorders* with 67 papers (2.07%) and *Diabetes Research and Clinical Practice* with 65 papers (2.01%).

Highly cited publications

A citation analysis of the retrieved publications revealed an average of 26.74 citations per article. The overall citation impact was further characterized by an h-index of 126 and a total cumulative citation count of 86355. The citation distribution was uneven. While 472 (14.6%) of the articles received no citations, 165 (5.11%) were highly cited, receiving > 100 citations each. The citation counts ranged from 0 to 1179. Table 5 details the top 10 publications associated with DM and depression, which together garnered 7632 citations. These top publications had citation counts ranging from 546 to 1179 [49-58].

Research hotspots and research themes

A visualization map based on frequent terms in the retrieved articles revealed three main research themes (Figure 3). The red cluster highlights a focus on understanding how depression and diabetes cooccur, with a growing interest in prevalence and contributing factors. This finding aligns with the emphasis on epidemiology and risk factors observed in this cluster. The green cluster centers on randomized controlled trials (RCTs) investigating how depression hinders diabetes management. These RCTs tested interventions such as psychotherapy, medication, or lifestyle changes to improve depression symptoms in diabetic patients, aiming for better diabetes control. Finally, the blue cluster explores the interplay of risk factors and mechanisms. This research examined how factors such as self-care decline, shared risk factors (obesity, inactivity), and potential biological and social mechanisms influence the two-way relationship between diabetes and depression.

DISCUSSION

The purpose of this study was to use bibliometric analysis to clarify the trends in research on depression and diabetes from 2004 to 2023. A total of 3229 relevant publications were obtained from Scopus. Subsequently, the bibliometric mapping program VOSviewer was used to show the primary characteristics and general landscape of the field's

Table 1 Top 10 countries publishing research on diabetes mellitus and depression from 2004 to 2023

Ranking	Country	No. of documents	%
1st	USA	1015	31.43
2nd	China	325	10.07
3rd	UK	236	7.31
4th	Germany	218	6.75
5th	Canada	175	5.42
6th	Netherlands	153	4.74
7th	Australia	150	4.65
8th	India	130	4.03
9th	Iran	102	3.16
10th	Brazil	98	3.03

Table 2 Top 10 active institutions in research related to the links between diabetes mellitus and depression from 2004 to 2023

Ranking	Institute	Country	No. of documents	%
1st	University of Washington	USA	87	2.69
2nd	Tilburg University	Netherlands	63	1.95
3rd	Université McGill	Canada	54	1.67
4th	Universiteit van Amsterdam	Netherlands	53	1.64
5th	VA Medical Center	USA	52	1.61
6th	Harvard Medical School	USA	51	1.58
7th	Amsterdam UMC - Vrije Universiteit Amsterdam	Netherlands	50	1.55
8th	King's College London	UK	44	1.36
9th	University of Michigan, Ann Arbor	USA	43	1.33
10th	Institut Universitaire en Santé Mentale Douglas	Canada	42	1.30

Table 3 Top 10 active funding agencies in research related to the links between diabetes mellitus and depression from 2004 to 2023

Ranking	Funding agency	Country	No. of documents	%
1st	National Institute of Diabetes and Digestive and Kidney Diseases	USA	189	5.85
2nd	National Institutes of Health	USA	153	4.74
3rd	National Institute of Mental Health	USA	125	3.87
4th	National Natural Science Foundation of China	China	91	2.82
5th	National Institute on Aging	USA	70	2.17
6th	Canadian Institutes of Health Research	Canada	44	1.36
7th	Bundesministerium für Bildung und Forschung	Germany	31	0.96
7th	National Heart, Lung, and Blood Institute	USA	31	0.96
9th	National Health and Medical Research Council	Australia	27	0.84
10th	Conselho Nacional de Desenvolvimento Científico e Tecnológico	Brazil	26	0.81

Table 4 Top 10 active journals in research related to the links between diabetes mellitus and depression from 2004 to 2023

Ranking	Journal	Frequency	%	IF[1]
1st	*Diabetes Care*	139	4.30	16.2
2nd	*Diabetic Medicine*	96	2.97	3.5
3rd	*Journal of Affective Disorders*	67	2.07	6.6
4th	*Diabetes Research and Clinical Practice*	65	2.01	5.1
5th	*Journal of Diabetes and Its Complications*	47	1.46	3.0
5th	*Plos One*	47	1.46	3.7
7th	*Diabetologia*	35	1.08	8.2
8th	*Journal of Psychosomatic Research*	34	1.05	4.7
9th	*General Hospital Psychiatry*	33	1.02	7.0
10th	*BMC Psychiatry*	32	0.99	4.4

[1]Impact factor based on Clarivate Analytics Journal Citation Reports 2022.
IF: Impact factor.

Table 5 The 10 most cited publications related to the links between diabetes mellitus and depression from 2004 to 2023

Ref.	Title	Year	Source title	Cited by
Mezuk *et al*[54]	Depression and type 2 diabetes over the lifespan: A meta-analysis	2008	*Diabetes Care*	1179
Ali *et al*[57]	The prevalence of co-morbid depression in adults with Type 2 diabetes: A systematic review and meta-analysis	2006	*Diabetic Medicine*	935
Roy and Lloyd [51]	Epidemiology of depression and diabetes: A systematic review	2012	*Journal of Affective Disorders*	809
Lin *et al*[55]	Relationship of depression and diabetes self-care, medication adherence, and preventive care	2004	*Diabetes Care*	795
Knol *et al*[53]	Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis	2006	*Diabetologia*	751
Gonzalez *et al* [56]	Depression and diabetes treatment nonadherence: A meta-analysis	2008	*Diabetes Care*	743
Golden *et al* [49]	Examining a bidirectional association between depressive symptoms and diabetes	2008	*JAMA*	694
Katon *et al*[58]	The pathways study: A randomized trial of collaborative care in patients with diabetes and depression	2004	*Archives of General Psychiatry*	609
Bixler *et al*[50]	Excessive daytime sleepiness in a general population sample: The role of sleep apnea, age, obesity, diabetes, and depression	2005	*Journal of Clinical Endocrinology and Metabolism*	571
Nouwen *et al* [52]	Type 2 diabetes mellitus as a risk factor for the onset of depression: A systematic review and meta-analysis	2010	*Diabetologia*	546

evolution. The overall publication output during the previous 20 years showed a dynamic trend that peaked in 2023. Additionally, we examined global collaboration, contributions to organizations, financing sources, journal publishing, and citations. Future directions for diabetes and depression research are also considered in the discussion.

The primary causes of the upward trend in the number of articles describing the links between depression and diabetes were as follows. The bidirectional relationship between depression and diabetes is a significant area of research that has contributed to the increasing trend of publications[4,59-62]. Several factors, such as a decrease in self-care, obesity and sedentary lifestyles, which are common risk factors, and the impact of depression on diabetes treatment have been related to depression and diabetes[60,61,63]. The bidirectional relationship between T2DM and depression has prompted interest in understanding the shared molecular processes of hyperglycemia, vascular dysfunction, and low-grade inflammation [8]. Clinical trials with large sample sizes, meta-analyses, and extensive national and cross-country clinical investigations are a few examples of how research methodologies have progressed to support the increase in publications[60]. The conditions of research in this field have been revealed through the use of bibliometric and visual analysis, highlighting popular topics and potential future research directions[64].

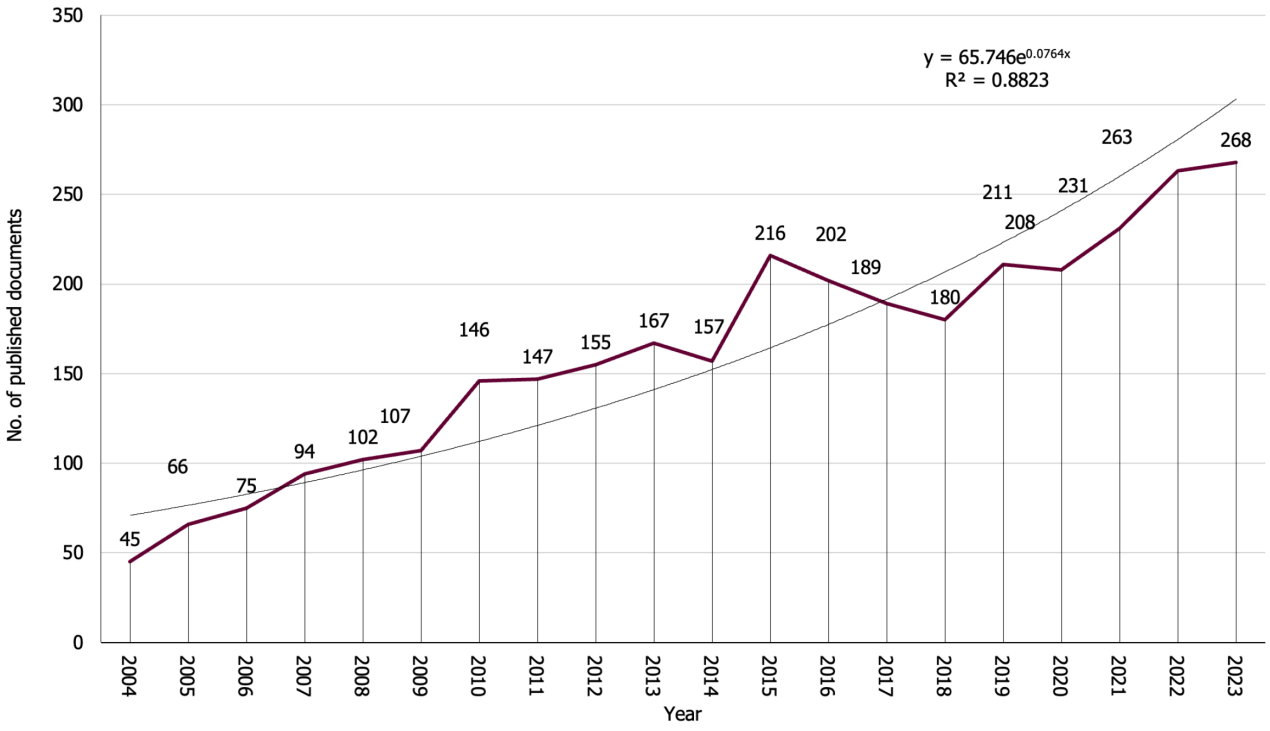

Figure 1 Annual growth of publications on the link between diabetes mellitus and depression.

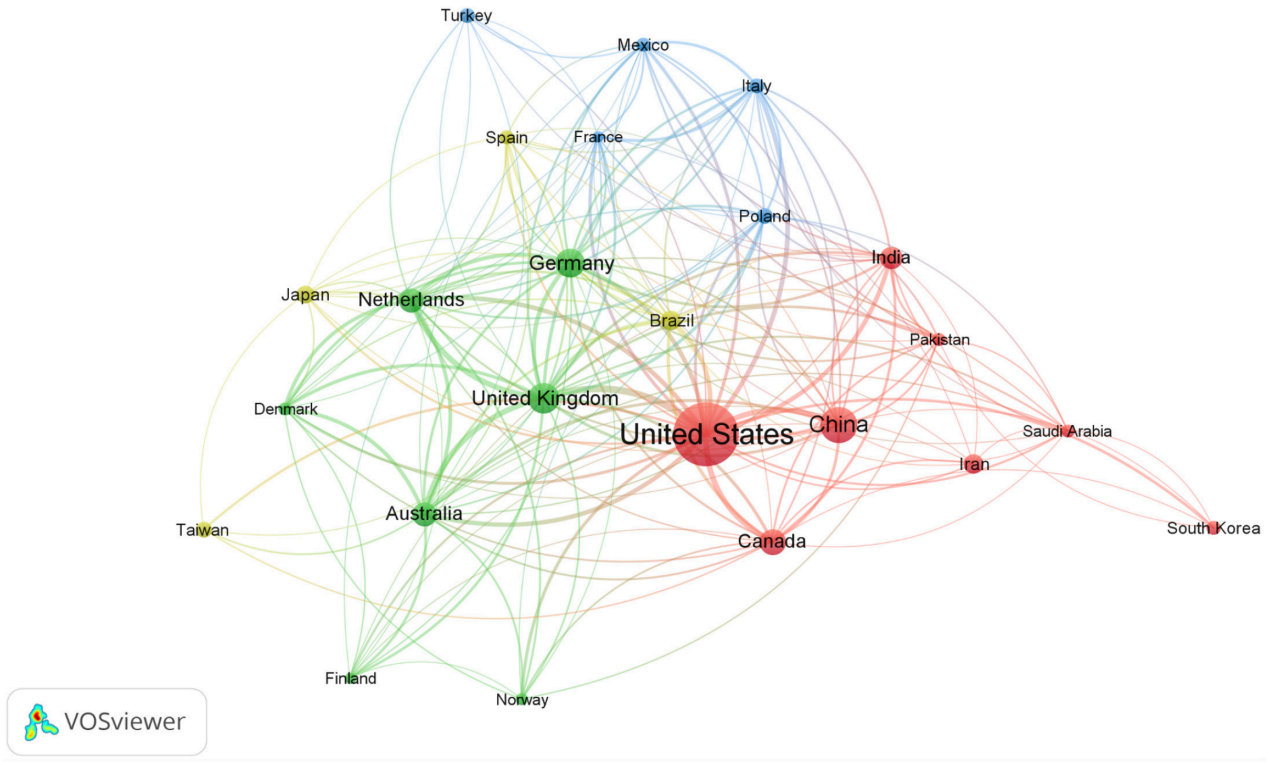

Figure 2 Mapping of international research collaborations on diabetes mellitus and depression from 2004 to 2023. Connections are highlighted with a minimum of 30 publications per country. Out of 160 active countries, 24 exceeded this threshold, with the node size reflecting the number of publications. The data were visualized using VOSviewer software version 1.6.20.

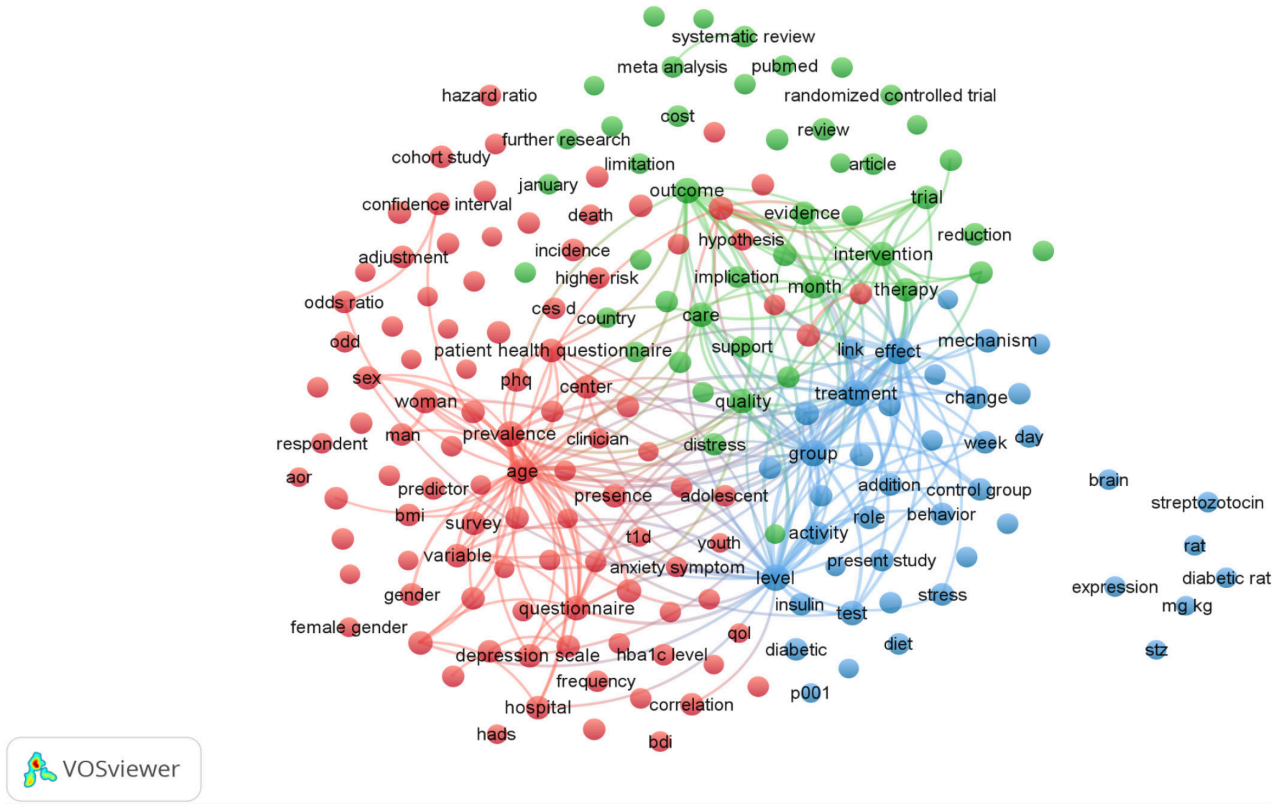

Figure 3 Mapping frequent terms in titles and abstracts to identify research themes in the field of diabetes mellitus and depression. Generated using VOSviewer software version 1.6.20, the map highlights 311 terms identified with a minimum-term occurrence threshold of 50 out of a total of 40 626 terms in the diabetes mellitus and depression domain. The terms are organized into three distinct clusters, each represented by a unique color, and the node size reflects the frequency of term usage across various publications.

We noticed that over time, the countries with the most publications on the links between diabetes and depression were the USA, China, and the UK. The USA had the most citations, field-weighted citation impact, and publications globally concerning endocrinology, diabetes, and metabolism[65]. The USA plays a prominent role in diabetes research and has the most active research facilities and researchers[64]. Diabetes research in China has attracted increasing amounts of attention due to the high prevalence of diabetes worldwide[66,67]. The country has made significant progress in diabetes research, both in terms of volume and publishing effect[68]. Additionally, the UK is significantly adding to the corpus of research in the fields of endocrinology, diabetes, and metabolism[65]. It is one of the countries with the greatest number of publications and citations in this field[65].

Actively studied topics can be identified *via* term clustering and co-occurrence analysis. Three subjects have been thoroughly researched during the last 20 years. The first cluster emphasizes the growing attention given to the prevalence and contributing factors of the coexistence of depression and diabetes. This result supports the focus on epidemiology and risk factors that this cluster identified. RCTs examining how depression affects diabetes management made up the second cluster. These RCTs aimed for better diabetes control and assessed treatments, including psychotherapy, medication, or lifestyle modifications, for minimizing depression symptoms in diabetic patients. The third cluster investigated how risk factors and mechanisms interact. The present study investigated the possible biological and social mechanisms affecting the two-way relationship between diabetes and depression, as well as shared risk factors (obesity and inactivity).

The co-occurrence of depression and diabetes is an important issue, and there is increasing interest in their prevalence and contributing risk factors. There is evidence pointing to common biological processes between T2D and depression, and depression is twice as common in those with this disease as in the general public[8,60]. In those with T2DM, comorbid conditions, dysglycemia, gender, anxiety, educational level, socioeconomic status, and pharmaceutical treatments are among the factors that contribute to the onset of cognitive impairments, depression, and psychosocial problems[69]. Lifestyle decisions and social factors are important co-occurrence predictors, as are behavioral indicators, life outcomes, and demographic characteristics[70,71].

Another area attracting much interest is RCTs that look at how depression affects diabetes management. Cognitive behavioral therapy (CBT) helps people with T2DM better manage their depressive symptoms and diabetes[72-78]. CBT has been shown to improve glycemic control, quality of life, and self-care behavior in people with T2DM and to greatly decrease depressive symptoms and diabetes-related distress[73-75,77,78]. In adults with type 1 DM (T1DM) or T2DM, CBT-based therapies have been shown to improve glycemic control and depression symptoms in numerous RCTs[74,76-78]. Treatments such as CBT have been demonstrated in RCTs to lower both diabetes control and depressive symptoms, confirming the reciprocal relationship between depression and diabetes[72-78]. Researchers have investigated the longit-

udinal relationships between depression and diabetes regimen distress (RD) through RCTs. The results show a covarying link in which changes in RD and depression symptoms occur together over time[79]. RCTs have shown that CBT improves depressive symptoms, anxiety, stress associated with diabetes, glycemic control, quality of life, and self-care behavior in patients with T1DM or T2DM, advancing our knowledge of the possible advantages of CBT in diabetes[75-78]. We should exercise caution when interpreting RCT findings due to the heterogeneity in CBT delivery methods, follow-up duration, outcomes, and long-term effects[73,75]. Considering the great variety of included studies and other limitations, more studies with a large number of studies are necessary to validate the findings[74]. The feasibility and efficacy of collaborative care models for depression in diabetes patients in low- and middle-income countries are yet unknown, which emphasizes the need for ethical issues while carrying out RCTs in various geographic locations[80]. A multicenter single-blind RCT emphasized the need for ethical issues when carrying out RCTs on comorbid depression and diabetes in diverse populations[80]. Its goal is to determine the efficacy of fluoxetine and mindfulness in primary care settings.

Researchers are currently investigating potential biological and social factors that influence the inverse relationship between diabetes and depression. Numerous studies have demonstrated a bidirectional relationship between diabetes and depression, influenced by both biological and social factors. Biological processes such as hyperglycemia, vascular dysfunction, and inflammation are linked to T2D and depression, with depression being twice as common in T2D patients as in the general population[8,81]. It is possible that inflammation, sleep problems, a sedentary lifestyle, poor eating habits, and activation of the HPA axis are at the root of both disorders[81]. The somatic-affective aspect of depression primarily links diabetes and depression, and the use of somatic health care independently links both disorders [82,83]. Common biological and behavioral processes, such as inflammation, autonomic dysfunction, sleep disturbance, an inactive lifestyle, poor eating habits, environmental and cultural risk factors, and activation of the HPA axis, are linked to depression and diabetes[7].

Future research directions for exploring the links between diabetes and depression are likely to focus on mechanistic studies to understand the molecular mechanisms underlying the bidirectional relationship[59]. To determine whether treating patients with comorbid conditions will enhance their quality of life and medical outcomes, lengthy, outcome-oriented RCTs are required[60]. Future research should focus on identifying promising preventive interventions and creating creative, cost-effective interventions to prevent depression, T2DM, and cardiovascular diseases[84].

This innovative study established the first baseline data on research activities investigating the link between DM and depression. However, some limitations are important to consider. First, relying solely on Scopus for document retrieval may have excluded relevant publications from local, unindexed journals. While Scopus is a vast database, numerous health-related publications, particularly from non-English-speaking countries, might not be indexed. This can introduce bias toward countries with well-represented journals or English-language publications, potentially underestimating overall research productivity. Second, the analysis was restricted to publications retrieved from Scopus, potentially limiting its comprehensiveness. However, Scopus remains the most accessible database for analyzing research activity and identifying hotspots on specific topics. Finally, the search terms were confined to "DM and depression" and related terms within titles only. This approach might have missed relevant publications that used these terms as keywords or within the body of the text.

CONCLUSION

This study examined the development, patterns, and areas of inquiry related to depression in diabetes patients. An examination of 3229 publications released between 2004 and 2023 revealed a significant increase in research efforts during the previous 20 years, highlighting the significance of treating this common psychological disorder in individuals with diabetes. Due to their substantial contributions to diabetes research and the significant influence of their publications in the field, the USA, China, and the UK emerged as the top three countries with the highest volume of publications regarding the relationship between depression and diabetes. The analysis delineated three principal themes in research on depression and diabetes: (1) Exploring the elevated prevalence and etiology of this comorbidity; (2) focusing on interventions, particularly RCTs, aimed at enhancing diabetes management among individuals with depression; and (3) investigating the involved risk factors and biological mechanisms underlying this bidirectional relationship. This research sheds light on the growing recognition of the influence of depression on treatment adherence and health outcomes within this demographic group. This study has contributed to advancing knowledge in this field by charting a course for future research on depression treatments for individuals with diabetes.

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FOOTNOTES

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LETTER TO THE EDITOR

Beyond surgery: Overcoming postoperative depression in cancer patients

Shao-Ming Song, Xiao Wang, Hong-Mei Yue, Rong Liu

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Abstract

Depression is a common occurrence among cancer patients, and it significantly impacts their clinical outcomes and quality of life, with a high incidence during anti-tumor treatment or after surgery. The association between surgery and depression is the result of the interaction of various factors, including physiological, psychological, and social factors, all of which are intertwined and make patients susceptible to depression after surgical treatment. Postoperative depression has a significant negative impact on many aspects of cancer patients, and it requires timely identification and intervention to improve the overall outcome.

Key Words: Depression; Surgery; Tumor; Anti-tumor therapy

Core Tip: Postoperative depression has a series of negative effects on the recovery, quality of life, and subsequent anti-tumor therapy in cancer patients. We should evaluate patients who experience depression or have a tendency toward depression following surgery in a timely manner. Surgeons should use a combination of approaches to comprehensively assess the patient's psychiatric status and take appropriate measures to help them deal with depression, leading to improved clinical outcomes.

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TO THE EDITOR

We reviewed the article titled "Depression and anxiety among cancer patients visiting a tertiary care cancer hospital", published in the *World Journal of Psychiatry*[1]. The investigators conducted a cross-sectional study of 220 cancer patients to assess the prevalence of depression and anxiety. In this study, 124 (56.4%) of them were diagnosed with mild depression, 70 (31.8%) with moderate depression, and 3 (1.4%) with severe depression. Depression is a common psychiatric disorder of cancer patients and it has a major negative impact. Many studies have shown that a high percentage of patients with tumors develop depression after surgery or during subsequent anti-tumor therapy[1-3].

Postoperative depression manifests as a series of psychological symptoms such as low mood, anxiety, negative thinking, and a loss of interest or pleasure that occurs in patients after surgical treatment[4]. There is a close relationship between surgery and depression, and the underlying reasons mainly include the following: (1) Patients experience pain, fear, anxiety, and other discomfort during the perioperative period, which may cause or worsen depressive symptoms; (2) Changes may occur in the patient's neuroendocrine system, such as increased cortisol level, which are associated with the occurrence of postoperative depression[5]; (3) Patients may have strong fears and are anxious about the consequences of malignant disease and surgery; and (4) The surgical treatment and subsequent management are costly, which may lead to financial difficulties for patients with cancer, and the impact of the postoperative recovery process on their work could further exacerbate this burden[6]. The association between surgery and depression is a result of the interplay of various physiological, psychological, and social factors that combine to make patients susceptible to depression after surgical treatment.

Postoperative depression has a series of negative impacts. Depressive symptoms can lead to a lack of motivation to engage in recovery activities after surgery, thereby prolonging the recovery time, and possibly also affecting the function of the immune system, making patients more susceptible to infection and complications. Depressive symptoms and physical discomfort during recovery interact with each other in a vicious cycle. Moreover, the depressive state may influence the patient's attitude and compliance toward anti-tumor treatment. Although there are significant individual differences among cancer patients, we have observed numerous successful cases in clinical practice. For example, advanced-stage cancer patients who did not have the opportunity for surgery but they did not give up and actively received antitumor treatment, subsequently experienced a continuous reduction of the tumor size that allowed surgical resection. Additionally, many patients with large liver cancers who actively underwent a combination of multi-scheme anti-tumor treatments after surgery, experienced postoperative recurrence rates that were not significantly different from the 2-year recurrence rates of patients with small tumors (< 5 cm). Our clinical experience also indicates that many patients experiencing depression doubt or refuse treatment and medication, leading to discontinuation of treatment and poor survival outcomes. Briefly, postoperative depression has a significant negative impact on many aspects of cancer patients, and it requires timely identification and intervention to improve overall outcome and quality of life.

Preventive or interventive strategies to reduce the impact of postoperative depression are important. Multiple methods are available to a surgeon to assess a patient with depression or depressive tendencies. Firstly, we should closely observe the patient's behavior, words, and emotional expression and pay attention to signs such as low mood, insomnia, change in appetite, obvious negative emotions, or other depressive tendencies preoperatively and postoperatively[7,8]. Standard psychological questionnaires or scales, such as the Generalized Anxiety Disorder Scale (GAD-7) and the Patient Health Questionnaire (PHQ-9), should be used when necessary[9]. The establishment of multidisciplinary teams of surgeons, anesthesiologists, and nurses helps to ensure adequate psychological assessment. Special attention must be given to patients who have a history of psychiatric disease, preoperative anxiety, complex surgery, or poor prognosis, as they are at higher risk for postoperative depression. When assessing these patients for depression, it is recommended to collaborate with professional psychologists or counselors who could provide deeper psychological evaluation. Use of these methods could comprehensively evaluate a patient's psychiatric status and take appropriate measures to help them deal with depressive emotions and improve clinical outcomes.

The success of intervention strategies requires building good communication and trusting relationships with patients and listening to them and their inner feelings. A healthy diet, moderate physical activity, restful sleep, and effective pain management are some of the things that can help improve depressive symptoms. Emotional support and encouragement from family and friends are also critical and can help patients participate in family and social activities[10]. Individualized interventions should be provided by a psychologist, if needed. The alleviation of postoperative depression or anxiety can be achieved with a variety of pharmacologic agents, such as selective 5-hydroxytryptamine reuptake inhibitors and benzodiazepines[11]. When using these medications, the patient's overall health and specific situation, including drug side effects and interactions need to be considered. Nonpharmacological therapies that help alleviate postoperative depression include cognitive behavioral therapy, music therapy, and social support[7,12]. In summary, it is essential to increase attention to and research on postoperative depression in the future. Effective identification and intervention should include multiple settings to provide comprehensive psychological support that improves long-term survival and the quality of life.

FOOTNOTES

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