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EDITORIAL

First 150 years of catatonia: Looking back at its complicated history and forward to the road ahead

Levente Csihi, Gabor S Ungvari, Stanley N Caroff, Gábor Gazdag

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Abstract

Karl Ludwig Kahlbaum (1828-1899) was the first to conceptualize and describe the main clinical features of a novel psychiatric illness, which he termed catatonia in his groundbreaking monograph published 150 years ago. Although Kahlbaum postulated catatonia as a separate disease entity characterized by psychomotor symptoms and a cyclical course, a close examination of his 26 cases reveals that most of them presented with motor symptom complexes or syndromes associated with various psychiatric and medical conditions. In his classification system, Kraepelin categorized catatonic motor symptoms that occur in combination with psychotic symptoms and typically have a poor prognosis within his dementia praecox (schizophrenia) disease entity. Because of the substantial influence of Kraepelin's classification, catatonia was predominantly perceived as a component of schizophrenia for most of the 20th century. However, with the advent of the psychopharmacotherapy era starting from the early 1950s, interest in catatonia in both clinical practice and research subsided until the early 2000s. The past two decades have witnessed a resurgence of interest in catatonia. The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, marked a paradigmatic shift

by acknowledging that catatonia can occur secondary to various psychiatric and medical conditions. The introduction of an independent diagnostic category termed "Catatonia Not Otherwise Specified" significantly stimulated research in this field. The authors briefly review the history and findings of recent catatonia research and highlight promising directions for future exploration.

Key Words: Catatonia; Historical overview; Psychopharmacology; Diagnostic and Statistical Manual of Mental Disorders-5; Wernicke-Kleist-Leonhard school

Core Tip: With the advent of the psychopharmacotherapy era starting from the early 1950s, interest in catatonia in both clinical practice and research subsided until the early 2000s. The past two decades have witnessed a resurgence of interest in catatonia. The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, marked a paradigmatic shift by acknowledging that catatonia can occur secondary to various psychiatric and medical conditions. The introduction of an independent diagnostic category termed "Catatonia Not Otherwise Specified" significantly stimulated research in this field.

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INTRODUCTION

Over the past 150 years, the definition, clinical assessment, and diagnosis of catatonia have followed a long and winding path. The 150th anniversary of the first scientific description of catatonia by Kahlbaum provides an excellent opportunity to summarize the evolution of the concept and current understanding of its myriad manifestations and neurobiological correlates, emphasizing its clinical importance and exploring future directions for catatonia research.

FORMATION AND DEVELOPMENT OF THE CONCEPT OF CATATONIA

Kahlbaum[1] (1828-1899) was the first to conceptualize and describe the main clinical features of a new psychiatric illness, which he termed catatonia in his groundbreaking monograph published in 1874. He defined catatonia as "a brain disease with a cyclical, fluctuating course, in which successive mental symptoms are melancholia, mania, stupor, confusion, and finally dementia. In addition to mental symptoms, motor nervous (systemic) processes also appear, the typical symptoms of which are usually epileptic in nature". He described 17 motor and psychomotor abnormalities, collectively designated as "movement stereotypes" and unified them into a new clinical entity. In addition, Kahlbaum was a pioneer of psychiatric nosology, being the first to emphasize the fundamental importance of longitudinal observations and disease outcomes and to distinguish the disease process (Krankheitsprozess) from the cross-sectional presentation (Zustandsbild), effectively separating the presenting syndrome from the presumed underlying disease entity. Although Kahlbaum postulated catatonia as a separate disease entity characterized by psychomotor symptoms and a cyclical course, a close examination of his 26 cases reveals that most of them presented with motor symptom complexes or syndromes associated with various psychiatric and medical conditions.

Kraepelin[2] sought to establish the position of catatonia in psychiatric nosology in a different way. He postulated that psychiatric illnesses primarily result from biological and genetic disorders. Kraepelin[2] introduced the concept of dementia praecox, defining it as "a semi-acute development of a peculiar state of mental weakness occurring at a young age". In his initial presentation of this concept in 1893 in the fourth German edition of his "Compendium der Psychiatrie" [3], he placed it alongside degenerative disorders but separately from catatonia and paranoid dementia. However, in 1899, in the sixth edition of the Compendium, Kraepelin[4] treated all three clinical types (hebephrenia, catatonia, and paranoid dementia praecox) as different expressions of a single disease, dementia praecox. According to Kraepelin's description, catatonia did not follow a sequential course; it exhibited an acute onset and was primarily defined by prominent positive psychotic symptoms, such as delusional preoccupations and hallucinations. Furthermore, it often culminated in dementia for over half of his patients, whereas others displayed varying degrees of lasting behavioral and/or motor "peculiarities". Although acknowledging that catatonic signs and symptoms can manifest in various psychiatric disorders, it was Kraepelin, according to Kendler[5], who positioned catatonia primarily as a subtype of his newly proposed diagnostic entity, dementia praecox, a form of acute onset psychosis in young individuals that rapidly progressed toward dementia.

Because of the substantial influence of Kraepelin's classification, catatonia was predominantly viewed as a component of schizophrenia for most of the 20th century. Catatonic manifestations unrelated to schizophrenia, although recognized,

were absent from international diagnostic classifications[6]. The contribution of the Wernicke-Kleist-Leonhard school to the description and classification of catatonia has received scant attention in the international literature. Following the neuropathological and clinical traditions established by Carl Wernicke (1856-1906) and Karl Kleist (1879-1960), Karl Leonhard (1904-1988) devised a comprehensive description and nosology of catatonia based on painstakingly meticulous and dispassionate observation of patients over several decades. Drawing on personally conducted interviews, long-term follow up and family genetic studies of mostly chronic psychotic patients, Leonhard delineated seven sharply circumscribed catatonia subtypes, each with prognostic implications[7,8]. Yet, in spite of its great heuristic value, Leonhard's classification has always been pursued only by a small group of devotees and up to very recently, has never been subjected to vigorous scientific scrutiny exploring its validity apart from its periodic catatonia category[9,10].

In his 1934 review, Karl Heinz Stauder (1905-1969) described 27 cases of catatonia emerging in the context of acute febrile states[11]. These cases typically began with sudden and purposeless excitation, which then evolved into an exhausted stuporous state with severe confusion and key catatonic symptoms, such as hypertonic hypokinesia, posturing, and mutism. If untreated, patients remained in this final stuporous state for a maximum of 4 d, wherein cardiovascular and/or respiratory failure resulted in coma and eventually death. This variant of catatonia is referred to as Stauder's lethal catatonia[12] or pernicious or malignant catatonia[13]. This condition can also have iatrogenic origins, such as neuroleptic-induced catatonia, neuroleptic malignant syndrome, toxic serotonergic syndrome, or, as a more recently discovered cause, autoimmune [*e.g.*, anti-N-methyl-D-aspartate (NMDA) receptor] encephalitis[14].

With the advent of the psychopharmacotherapy era starting from the early 1950s, interest in catatonia subsided in clinical practice and research until the early 2000s. Most American psychiatrists mainly relied on Kraepelin's and Bleuler's concepts of catatonia. In the first three editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM)[15-17] published by the American Psychiatric Association, catatonia only appeared as a subtype of schizophrenia; this approach likely resulted in significant neglect, underdiagnosis and inadequate treatment of catatonia[18,19].

Two seminal studies by American authors[20,21] reshaped the understanding of catatonia in American psychiatry. In a prospective 14-month study involving 55 patients with catatonia, only a quarter of the patients met the DSM criteria for schizophrenia, whereas approximately two-thirds of them developed affective disorders, predominantly mania, and nine of the patients were diagnosed with a neurological condition[20]. Catatonic signs and symptoms were present in similar proportions across all three groups. Gelenberg took the findings of Abrams and Taylor one step further by offering a well-researched and poignant appeal to the scientific community. In a seminal review, Gelenberg[21] documented the occurrence of catatonia across diverse etiological conditions essentially challenging the narrow general understanding of catatonia as subtype of schizophrenia and establishing it as a syndrome that extended across diagnostic boundaries. This shift in the conceptualization of catatonia was reflected in the fourth edition of the DSM[22], leading to the inclusion of two new categories: (1) Catatonia secondary to a general medical condition; and (2) catatonic features as specifiers of mood disorders. The classification of catatonia as a subtype of schizophrenia remained unchanged. The presence of a minimum of 2 out of a total of 12 catatonic signs and symptoms was required to make a diagnosis of catatonia. Further refinement in DSM-5 led to the subdivision of catatonia into acute, chronic, cyclic, excited, retarded, and malignant forms [23]. It was also suggested that the etiology of catatonic symptoms, specifically the primary psychiatric or medical diagnosis, should be reflected in the diagnostic scheme, given their therapeutic and prognostic implications[23].

The past two decades witnessed a resurgence of interest in catatonia. In the DSM-5[24], there was a notable change in the paradigm regarding catatonia. It was recognized that catatonia can be secondary and can occur within a wide range of psychiatric and medical conditions. The manual no longer listed catatonia as a form of schizophrenia. Instead, catatonia is classified as a syndrome occurring in three major settings: (1) Catatonic disorder due to a general medical condition; (2) catatonia as a specifier for 10 mood and psychotic disorders (including schizophrenia); and (3) catatonia not otherwise specified. The introduction of the last category opened the possibility of considering catatonia as an independent, separate entity, significantly stimulating research in this field[18]. To establish a diagnosis, clinicians must observe 3 out of the 12 catatonic signs or symptoms within a month, potentially yielding thousands of possible combinations of symptoms and signs that all lead to the same general unitary diagnosis of catatonia, without distinguishing between different phenotypical or clinical variants of catatonia.

RESEARCH DEVELOPMENTS IN THE FIELD OF CATATONIA

Over the past two decades, the number of publications reporting results of studies on catatonia and the number of articles published following the release of DSM-5 have increased dramatically. Despite these efforts, many questions regarding catatonia remain unanswered.

Since 1991, seven catatonia rating scales have been developed: the Modified Rogers Scale, Rogers Catatonia Scale Revised, Bush-Francis Catatonia Rating Scale, Northoff Catatonia Rating Scale, Catatonia Rating Scale, Braunig Catatonia Rating Scale and Kanner Scale[25]. All of these are generic scales based on the assumption that the composition and time frame of the catatonic syndrome remain the same irrespective of the underlying primary medical or psychiatric conditions. The aforementioned seven scales differ from each other in terms of the definitions and number of catatonic signs and symptoms they incorporate. Thus, the frequencies of catatonia cases measured using these different rating scales can vary substantially, ranging from 3.4% to 10.3%[26]. Given that various theoretical frameworks, nosological concepts, and rating scales/criteria used to diagnose catatonia have changed over time, comparing results using different scales is challenging. Comparisons are further complicated by the lack of a uniform procedure or definition for the time frame over which ratings are recorded, although some of the diagnostic criteria and the measurement scales also contain temporal and longitudinal factors.

Biological research in this field has a rich history. For instance, Rolv Gjessing and Leiv Gjessing described nitrogen disturbances and serum glucose and white blood cell abnormalities in phases of periodic catatonia and highlighted the therapeutic effect of thyroid extracts in some patients[27].

More recently, studies have explored the neurobiological underpinnings of catatonia using advanced imaging techniques[28-30]. Structural magnetic resonance imaging studies have revealed that catatonia was associated with widespread reductions in gray-matter volume, including in the orbitofrontal, cingulate, and visual cortices and the insula when compared with healthy individuals. Patients with catatonia demonstrated hypergyrification in the motor, premotor, and somatosensory cortices compared with controls; however, no differences in cortical thickness were observed between patients with catatonia and controls[29]. In addition, patients with catatonia were found to have significantly smaller volumes in the anterior inferior hypothalamus, the cortical nucleus of the amygdala, and the hippocampal fimbria[30]. Furthermore, patients with catatonia exhibited poor functional activation of the supplementary motor area, primary and secondary motor cortices, inferior parietal cortex, and basal ganglia during self-initiated movements[31,32]. Studies have observed reduced cerebral blood flow in the right prefrontal and parietal cortices[33] and reduced GABA-A-receptor density in the left sensorimotor cortex[34]. Dysfunction in the orbitofrontal cortex could contribute to poor connectivity in the medial prefrontal cortices[35]. An arterial spin labeling study showed that patients with schizophrenia exhibited increased cerebral blood flow in the left primary motor cortex and supplementary motor area during a catatonic episode[36]. In addition, a transcranial magnetic stimulation (TMS) study of a patient with acute catatonia and echolalia revealed a "hyper-imitative" state that may account for echo-phenomenon observed in catatonia. TMS-induced hand muscle evoked potentials were higher when the subject watched hand movements involving those muscle groups compared to the resting state. However, this effect disappeared after the resolution of catatonia and echolalia, suggesting that specialized "mirror" neurons of motor and premotor cortices that fire during both action performance and action observation are disinhibited during a catatonic episode. Observations in this case report have raised intriguing questions and require further research[37]. At present, imaging techniques are research tools only and not of practical use for identifying catatonia other than excluding underlying structural brain lesions that are suspected based on clinical findings.

In genetic studies, the lifetime morbidity risk of catatonia in the first-degree relatives of patients with periodic catatonia was found to be 27%, with an autosomal dominant linkage to chromosome 15q15 and a heterogeneous linkage to chromosome 22q13[38,39]. Preliminary evidence indicates that a more severe catatonic syndrome in patients with schizophrenia is associated with a loss-of-function allele of a myelin-specific gene[40]. In animal studies, D2-receptor-deficient mice showed severe motor abnormalities, including aberrant locomotor initiation and spontaneous catatonia[41,42]. While no chromosomal variants have been consistently tied to catatonia, further studies may prove informative in identifying pathophysiology, enabling targeted treatment development, and identifying patients at risk.

In epidemiological studies, the incidence of catatonia in adult inpatients with psychiatric conditions was estimated to be approximately 10%[43-45]. However, the prevalence of catatonia varied substantially based on underlying or comorbid conditions, ranging from 4% to 67% in schizophrenia, from 14% to 71% in mood disorders, from 4% to 46% in medical conditions[46], and from 6% to 20.2% in neurodevelopmental disabilities[47]. Among hospitalized children, the incidence of catatonia was 4%[48].

Patients with catatonia exhibited decreased serum iron levels and increased creatine kinase and NMDA-receptor antibodies[49]. Iron levels serve as a negative acute phase reactant and tend to be low in acute inflammatory states and numerous autoimmune disorders. Thus, it is hypothesized that catatonia is associated with central and peripheral inflammation[50].

Several studies have focused on catatonia in specific populations, including children[47], adolescents[51], older individuals[52,53], and women in the peripartum period[54,55].

Advances in the management of catatonia remain primarily based on clinical and observational evidence rather than controlled trials. Nevertheless, the lorazepam challenge test is accepted as a useful tool not only to treat catatonia, but also to confirm its diagnosis. The gold standard for the treatment of catatonic symptoms is still lorazepam or other benzodiazepines. If benzodiazepines proved to be ineffective, then electroconvulsive therapy (ECT) is the second option [56]. If psychosis is the underlying cause of catatonia, second generation antipsychotics could be used with caution due to the risk of inducing neuroleptic malignant syndrome[57]. If the patient does not respond to the above-mentioned therapeutic interventions, then an NMDA-receptor antagonist could be a possible choice. When ECT is not available, new neurostimulation techniques, *e.g.*, TMS or direct current stimulation could be alternatives for pharmacotherapy-resistant cases[56].

FUTURE RESEARCH DIRECTIONS

The first and most important research imperative involves achieving a consensus-based harmonization of the concept and symptoms of catatonia. This harmonization is necessary to improve the diagnostic process and standardize results between studies to enable systematic comparisons and meta-analyses. In addition, it is important to determine the longitudinal course of diverse catatonic phenotypes and the time frame in which the presence of catatonic symptoms is required for a diagnosis. Neural mechanisms underlying catatonia remain unknown. Advances in genetics as well as structural and functional imaging techniques can provide a deeper understanding of the neurobiological correlates of catatonia[28]. Furthermore, research on experimental animal models of catatonia is still in its initial stages, and their development appears to be a promising avenue for further research that is unique in research of behavioral conditions [47]. In addition, investigations and research into innovative pharmacological and neuromodulatory treatments are still in

their early stages[58,59].

CONCLUSION

Catatonia has garnered substantial renewed interest in psychiatry over the past two decades, with a notable surge following the publication of DSM-5. The development of the concept and diagnosis of catatonia has undergone a remarkable journey over the last 150 years, and this journey is still ongoing. Several international research groups are actively investigating the theoretical, diagnostic, and neurobiological aspects of catatonia. Their aim is to translate research findings into clinical practice to improve the rate and speed of recovery and the quality of life of patients with catatonia.

FOOTNOTES

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REVIEW

Exploring the transformative impact of traditional Chinese medicine on depression: Insights from animal models

Yan Yang, Yan-Kun Chen, Meng-Zhou Xie

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Abstract

Depression, a prevalent and complex mental health condition, presents a significant global health burden. Depression is one of the most frequent mental disorders; deaths from it account for 14.3% of people worldwide. In recent years, the integration of complementary and alternative medicine, including traditional Chinese medicine (TCM), has gained attention as a potential avenue for addressing depression. This comprehensive review critically assesses the efficacy of TCM interventions in alleviating depressive symptoms. An in-depth look at different research studies, clinical trials, and meta-analyses is used in this review to look into how TCM practices like herbal formulations, acupuncture, and mind-body practices work. The review looks at the quality of the evidence, the rigor of the methods, and any possible flaws in the current studies. This gives us an idea of where TCM stands right now in terms of treating depression. This comprehensive review aims to assess the efficacy of TCM interventions in alleviating depressive symptoms. In order to learn more about their possible healing effects, the study also looks into how different types of TCM work, such as herbal formulas, acupuncture, and mind-body practices.

Key Words: Traditional Chinese medicine; Depression; Efficacy; Treatment; Holistic approach

Core Tip: Traditional Chinese Medicine (TCM) emerges as a promising area for intervention in the face of the global health burden that depression poses. This review scrutinizes the efficacy of TCM in alleviating depression, delving into the intricate mechanisms behind herbal formulations, acupuncture, and mind-body practices. As one of the most prevalent mental disorders worldwide, depression demands innovative approaches, and the integration of complementary and alternative medicine offers a compelling avenue. Through evaluating research studies, clinical trials, and meta-analyses, this review not only assesses the current state of TCM in depression management but also its potential for transformative impact, bridging ancient roots with modern resilience.

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INTRODUCTION

Depression, a complex and pervasive mental health disorder, is one of our time's most prevalent and impactful global health challenges. Characterized by persistent sadness, loss of interest or pleasure, and a range of cognitive and physical symptoms, depression profoundly affects an individual's emotional well-being, daily functioning, and overall quality of life. With a global prevalence estimated at over 300 million people, depression is a leading cause of disability worldwide [1]. The first comprehensive statistical study of subthreshold depression prevalence estimates. According to the findings, 11.02% of the population displayed symptoms of mild-to-moderate depression. The youngest age group (14.17%) had the highest prevalence, followed by the oldest (12.95%) and then adults (8.92%)[2]. Depression is one of the most frequent mental disorders; deaths from it make up 14.3% worldwide. It is a multifaceted condition that can manifest in various forms, from mild to severe, and impacts people of all ages and demographics. It affects an individual's personal, professional, and social functioning. Depression can include persistent sorrow, loss of interest, sleep difficulties, and cognitive deficits. These symptoms can lower quality of life, work productivity, relationships, and healthcare use[3].

Depression has high direct healthcare costs, indirect costs from diminished work productivity, and intangible costs from human suffering. Depression has ripple effects on families, communities, and society, emphasizing the need for effective interventions and a thorough understanding of its repercussions[4]. Self-care measures and psychological therapy are recommended for those with mild to moderate depression as an initial course of treatment. Medication may be administered if the patient's condition does not improve. The effectiveness of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, and sertraline for this aim is diminished by their potentially harmful side effects [5]. Despite the advancements in conventional treatments, the prevalence of depression and the limitations of existing interventions have led to exploring complementary and alternative approaches, such as traditional Chinese medicine (TCM)[6].

Among these approaches, TCM has garnered attention for its holistic perspective and potential to provide novel avenues for alleviating depressive symptoms. TCM, rooted in ancient Chinese philosophies and practices, offers a holistic framework that views health as a harmonious balance between mind, body, and spirit[7]. This approach emphasizes the interconnection of various bodily systems, environmental factors, emotions, and energy flows. The holistic nature of TCM aligns with the multifaceted manifestations of depression. According to TCM principles, depression can be understood as a disruption in the flow of vital energy, or "qi", as well as imbalances in the yin and yang forces within the body[8]. TCM encompasses a spectrum of modalities, including herbal remedies, acupuncture, dietary therapies, and mind-body practices such as Tai Chi and Qigong, each targeting specific aspects of these imbalances. The integration of these modalities is believed to restore harmony and enhance overall well-being[9].

In recent years, there has been growing interest in evaluating the efficacy of TCM interventions for depression. As conventional treatments may not provide satisfactory outcomes for all individuals, the potential of TCM to offer alternative or complementary strategies is gaining recognition. Several studies have investigated the effects of TCM modalities on depressive symptoms, exploring their mechanisms of action and potential synergies with conventional treatments[10]. By addressing depression through a holistic lens that considers both physiological and psychological factors, TCM presents a unique perspective that has the potential to fill gaps in current treatment paradigms.

This comprehensive review seeks to delve into the existing body of research that examines the efficacy of TCM in alleviating depression. By critically analyzing a wide range of studies, clinical trials, and meta-analyses, this review aims to provide a comprehensive overview of the current state of TCM interventions for depression management. The review aims to contribute to a deeper understanding of TCM's role in mental health care by synthesizing empirical evidence and discussing underlying mechanisms. Additionally, it will shed light on potential areas for further research and integration of TCM modalities into conventional treatment approaches, offering insights into a more holistic and patient-centered

approach to depression management.

OVERVIEW OF TCM

Key principles and fundamental concepts of TCM

The goal of TCM, a medical practice with roots dating back at least 2300 years, is a form of alternative medicine that draws on the expertise of Chinese doctors for more than 3500 years. TCM can be divided into two primary classes: preparations and materials. Chinese herbal medicine (CHM) and its various parts are the primary constituents of TCM materials[11]. Most TCM preparations consist of Chinese patent medicine, TCM granules, and various TCM clinical preparations. Although acupuncture and herbal remedies have been used for at least 2,200 years, the first recorded account of Chinese Medicine is found in the Huangdi Neijing (The Yellow Emperor's Inner Classic) from the third century BCE[12].

TCM is deeply rooted in a holistic understanding of health and well-being, guided by key principles and fundamental concepts that have shaped its philosophy for centuries. The concepts of Yin and Yang are central to TCM's worldview, representing opposing yet interconnected forces that are integral to all aspects of existence[13]. Yin embodies darkness, passivity, and coolness, while Yang embodies light, activity, and warmth. Health is seen as the harmonious balance and dynamic interplay between these opposing forces, and any disruption in this balance is thought to lead to illness[14]. Another cornerstone of TCM is the concept of Qi (pronounced "Chee"), often described as vital energy or life force. Qi flows through meridian channels, sustaining all bodily functions and maintaining a harmonious equilibrium. Health is maintained when Qi flows smoothly and unobstructed, but blockages or imbalances in this flow can lead to discomfort or disease. TCM interventions, such as acupuncture and herbal remedies, aim to restore the balanced flow of Qi throughout the body[15].

The Five Elements Theory is another fundamental concept in TCM that illuminates the intricate relationships and interdependencies in the natural world and the human body. This theory identifies five elements – Wood, Fire, Earth, Metal, and Water – each embody distinct qualities, attributes, and associations. These elements are not merely static components but dynamic forces that influence and regulate various aspects of health and well-being[16]. In TCM philosophy, the Five Elements represent universal energies that manifest within the human body and its surroundings. Each element is linked to specific organs, tissues, emotions, seasons, colors, and tastes. The interactions between the elements are characterized by two primary cycles: The Generating Cycle and the Controlling Cycle[17]. The Generating Cycle illustrates how each element nourishes and supports the subsequent one. For instance, Wood generates Fire, Fire generates Earth, Earth generates Metal, and Metal generates Water[18]. On the other hand, the Controlling Cycle elucidates how elements can exert influence over one another, maintaining a harmonious balance. For instance, Wood controls Earth, Earth controls Water, Water controls Fire, Fire controls Metal, and Metal controls Wood[19].

The Five Element Theory is a valuable diagnostic and treatment tool in TCM practice. By analyzing an individual's constitution and identifying patterns of imbalance among the elements, practitioners can tailor interventions to restore harmony and well-being. This holistic approach recognizes the interconnectedness of bodily functions, emotions, and environmental factors, offering a comprehensive perspective on health and illness beyond the physical[20]. As a result, the Five Element Theory plays a pivotal role in guiding TCM practitioners in their pursuit of optimal health and balance for their patients. There are numerous traditional Chinese remedies available that can help restore balance. Acupuncture, moxibustion, and cupping techniques stimulate blood flow to the skin[21]. According to Sankararaman *et al*[22] Chinese healers recommend a beverage prepared using a wide range of therapeutic herbs or dried animal parts, such as snakes, scorpions, insects, and deer antlers.

TCM is based on the concept of Qi, also known as vital breath, which is believed to flow through meridians that are not visible to the naked eye. According to Ji *et al*[23], this energy network connects components such as organs, tissues, veins, nerves, cells, atoms, and consciousness. In TCM, there are 12 primary meridians that each correspond to a specific organ. According to Jin *et al*[24], meridians create additional networks that are not visible. These networks are influenced by circadian rhythms, seasons, and planetary movements.

Primary TCM treatment modalities for depression

Music therapy using the five elements: TCM encompasses the five elements of music therapy, a treatment modality rooted in traditional Chinese music and influenced by the philosophical concepts of Yin Yang and the five elements. The five musical tones, namely Jiao, Zhi, Gong, Shang, and Yu, symbolically correspond to the five internal organs, namely the liver, heart, spleen, lung, and kidney, as well as the five associated emotions, namely anger, joy, anxiety, concern, and fear[25]. By balancing the Yin and Yang energies and regulating the circulation of Qi and blood within the human body, this practice has various functions. It can alleviate feelings of depression and nourish the liver, promote a sense of calmness in the heart and mind, regulate Qi and eliminate phlegm, strengthen the spleen and enhance blood nourishment, as well as nourish the Yin energy of the kidneys. Using a database search, Li *et al*[26] discovered that music, yoga, massage, and exercise help reduce sadness in expectant patients, with five-element music having the most therapeutic impact. The study by Park *et al*[27] examined the implications of five-element music therapy on brain wave α in depressed patients. The study discovered that five-element music therapy could enhance α waves, which are linked to depression, and alleviate depression and anxiety symptoms in treating depression.

In a study, Yang *et al*[28] employed a combination of five therapeutic components, including music and acupuncture, to treat female individuals diagnosed with depression. The research findings indicate that integrating several therapeutic approaches resulted in a notable decrease in symptoms of sadness, anxiety, and adverse emotional reactions. Patients

with post-stroke depression were randomly allocated to the control or treatment groups by Wang *et al*[29]. Primary care was provided to both groups, while music therapy with five components was given to the therapeutic group. The study discovered that participants' symptoms of depression were reduced by five-element music therapy. Long treatment cycles for depression are unstable and prone to recurrence.

Additionally, antidepressants are costly. Patients sometimes discontinue treatment due to financial hardship and the treatment cycle. The 5 Elements Music therapy is effective for treating depression as it is not limited by time or place, making it more straightforward to accept by sufferers[30].

Emotion-driven therapy: Medical professionals use emotion-led treatment to address patients experiencing abnormal emotions and psychological concerns, such as depression, doubt, anxiety, and low self-esteem. This approach focuses on non-drug interventions that restore the patient's emotional well-being and promote harmony in their overall energy (Qi) [31]. Several treatment methods are available, including environmental adaptation therapy, emotional guidance therapy, and language enlightenment. In their study, Petersson *et al*[32] implemented psychiatric counseling and mental nursing interventions in patients with depression. The results revealed that these interventions effectively reduced depressive symptoms and anxiety, ultimately improving the patient's overall state of life. Foroughe[33] implemented emotional nursing interventions for patients experiencing post-stroke depression, including providing empathy therapy. The findings indicated that emotional nursing interventions significantly impacted the patient's mental and psychological well-being.

In a study that Kashkouli *et al*[34] carried out, patients with moderate postpartum depression were divided into intervention and control groups. The control group received standard nursing care, whereas the intervention group received a structured psychological therapy intervention. The study's findings indicate that psychological counseling has demonstrated efficacy in alleviating symptoms of depression.

Acupuncture: Acupuncture, a cornerstone of TCM, presents a distinctive therapeutic approach to managing depression. During an acupuncture session, fine needles are meticulously inserted into specific acupoints along the body's meridians, aiming to regulate the flow of Qi, the vital life force. This process is believed to restore the balance of Yin and Yang energies within the body, addressing emotional and physical imbalances contributing to depressive symptoms[35]. By stimulating these acupoints, acupuncture is thought to alleviate the stagnation of Qi and promote its smooth circulation, facilitating the release of endorphins and other neurotransmitters that can enhance mood and alleviate emotional distress [36].

The acupuncture procedure for depression typically involves a personalized approach. Acupoints are carefully selected based on the individual's constitution, symptom presentation, and underlying energetic imbalances. Practitioners may focus on specific acupoints related to emotional well-being, stress reduction, and regulating vital organs such as the liver and spleen[37]. Moreover, acupuncture sessions are often accompanied by relaxation techniques to enhance the therapeutic experience. As a holistic approach, acupuncture addresses the interconnected nature of mind and body, acknowledging that emotional well-being is closely linked to the free flow of energy throughout the body's meridians. The practice of acupuncture in treating depression underscores the integration of Eastern healing wisdom into modern therapeutic strategies for mental health[38].

Acupuncture and associated therapies include acupuncture, electroacupuncture, warm acupuncture, and moxibustion. Acupuncture, often combined with moxibustion, forms a holistic therapeutic approach within TCM, utilizing needle stimulation and applying heat on acupoints by herb (Artemisia moxa cones) to balance Qi and enhance well-being. According to Ou *et al*[39], the utilization of database retrieval revealed that moxibustion and acupuncture interventions had demonstrated efficacy in reducing the severity of depression among patients diagnosed with depression. In a database analysis of 67 randomized controlled studies, Zhao *et al*[40] discovered that acupuncture helps alleviate depression problems such as nausea, diarrhea, and sleeplessness. By examining the animal model of depressed people, it was demonstrated that acupuncture could treat primary depression and lessen the adverse reactions of medications. Similarly, Zhao *et al*[41] conducted randomized trials to determine the effects of acupuncture and SSRIs on treating anxiety, somatization, sleep disturbances, and the depressive symptoms of moderate to severe depression.

A comprehensive meta-analysis involving the systematic search and screening of several databases determined that the combined administration of acupuncture and antidepressants yielded superior efficacy compared to using antidepressants in isolation. Pregnant women with depression received therapy by Abujilban *et al*[42] with standard care and acupuncture. The outcomes demonstrated that acupuncture was practical and efficient for enhancing mental wellness. Participants with mild to moderate depression have been treated with fluoxetine and ghost point acupuncture by Yang *et al*[43]. The findings demonstrated that acupuncture and pharmacological therapy can significantly enhance the clinical treatment's impact. Acupuncture offers the advantages of being less expensive and having fewer adverse effects than medication therapy. According to the survey, after six weeks, the effectiveness of various acupuncture treatments for treating depression ranges from 70% to 83.7%, comparable to or even higher than the effectiveness of antidepressant Western medicines. Acupuncture has a unique therapeutic impact on depression[44](Figure 1).

Nutritional therapy: Depression treatment can make use of nutrition. This is crucial because theories suggest that specific nutrients required for the brain's proper operation also impact the neurochemical and biological processes involved in the onset and course of depression. Additionally, there is growing research that links eating habits to the onset of severe depression and emphasizes the value of nutrition in preserving mental health. According to reports, the monoamines glutamate and Gamma-aminobutyric acid (GABA) linked to depression are synthesized due to food[45].

As more noradrenaline, dopamine, and serotonin, all required for mood regulation, are broken down, monoamine oxidase levels are likewise higher in depressed people. Essential for appropriate brain activities, polyunsaturated fatty acids, particularly omega-3 fatty acids, are standard cell membrane elements. The primary forms of -3 fatty acids are -

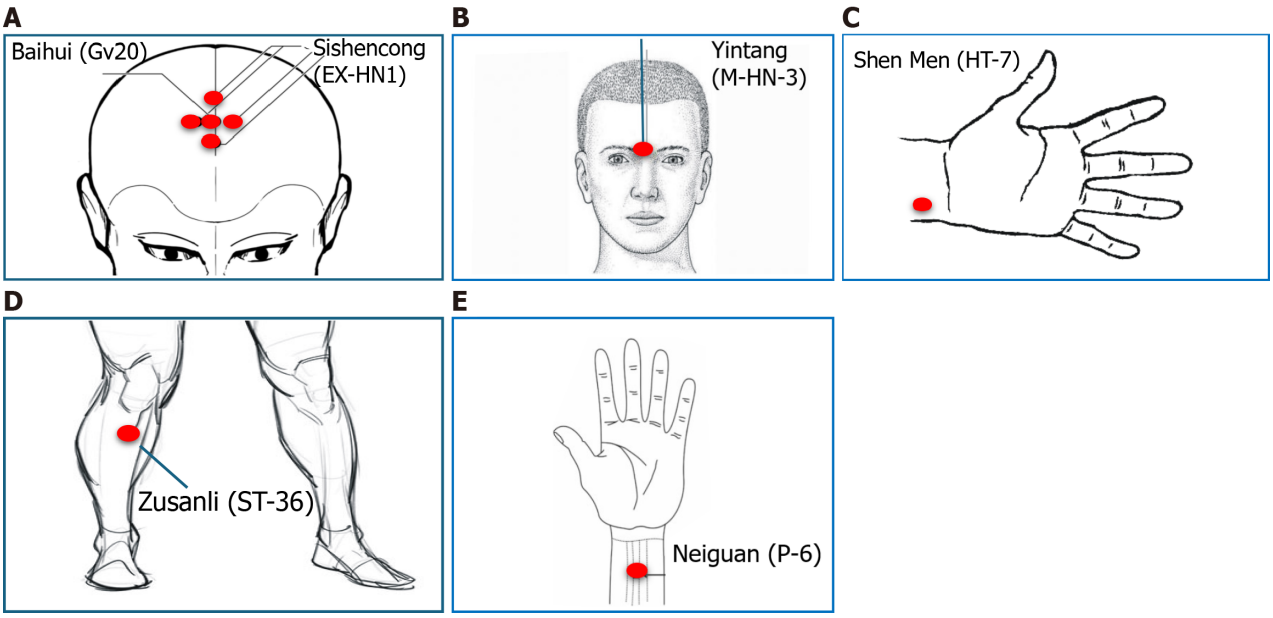

Figure 1 Acupuncture therapy for depression often involves targeting different acupoints. A: Stimulating Baihui is thought to disperse stagnant Qi and clear any emotional blockages; B: Stimulation of Yintang is believed to promote the free flow of Qi and blood; C: Stimulation of Shenmen is thought to regulate the Heart's Qi and blood circulation; D: Stimulation of Neiguan is thought to regulate the Pericardium's energy, helping to soothe emotional distress; E: Zusanli is associated with the Stomach meridian and is believed to influence physical and emotional well-being.

linolenic acid, which is primarily found in plants like canola oil, soy, and walnut, and the long-chain docosahexaenoic and eicosapentaenoic acids, which are most abundant in seafood[46]. Docosahexaenoic and eicosapentaenoic acids are abundant in fish, including sardines, anchovies, herring, mackerel, salmon, trout, and some eggs and animal products. High fish eating has been linked to lower depression risk.

Additionally, Protein insufficiency causes neurotransmitter and cognitive dysfunction. Tyrosine and tryptophan are precursors for synthesizing serotonin, while glutamate is the precursor for glutamate and GABA. Whole grains, almonds, oats, beans, fish, chicken, eggs, cheese, and milk are vital sources of tryptophan and tyrosine[47].

Poor tryptophan diets diminish brain serotonin, causing depression symptoms like anxiety, obsessions, and compulsions. Decreasing tryptophan levels can cause an abrupt depressive recurrence in remitted depressed patients. Tryptophan decreases depression-related stress and cortical chemicals[48]. Several studies show depressive patients consume less vitamins and minerals. Fruits, milk, poultry, eggs, lean meats, and fish are vitamin-rich. Vitamin A deficiency is linked to depression, but its role is unknown[49]. Strawberries, kiwi, guava, pepper, potatoes, tomatoes, citrus fruits, broccoli, and black currants contain vitamin C or ascorbic acid. Short-term vitamin C supplementation dramatically reduced anxiety and depression. Kiwi, mango, avocado, peanut, almond, sunflower, wheat germ oil, shellfish, and goose meat are vitamin E-rich fruits. Depressive symptoms decrease with vitamin E[50]. Furthermore, Individuals with depression have been found to have reduced levels of minerals such as zinc, iron, phosphorus, calcium, magnesium, potassium, and sodium. These lower levels are primarily linked to reduced intake of these minerals, either through supplements or in their diets[51].

Herbal therapy: In China, Japan, and Korea, CHM plays a crucial role in both TCM and conventional medicine. China's list of essential medications includes CHM injections, pills, capsules, and decoctions. TCM utilizes various herbs' healing properties to enhance the organs' functioning and promote overall wellness[52]. TCM practitioners can harness herbs' healing properties beyond their chemical and physical qualities. The practitioner carefully chooses the herbal mixture that aligns with the body's energy vibration. Chinese herbal formulas incorporate complementary ingredients[53]. TCM herbal formulations comprise plants with a wide range of therapeutic properties to aid the body in regaining balance. The Chinese apothecary categorized each plant part by its curative properties and gave them all names[54].

Sun *et al*[55] conducted a thorough study of scientific research on the antidepressant properties of herbal medicine and discovered 45 antidepressant herbal products using different *in vitro* and *in vivo* investigations. The antidepressant mechanisms may involve the participation of many signaling pathways that regulate the microbiota, endocrine system, antioxidation processes, anti-inflammation responses, neurogenesis, and neurotransmitter activity. Importantly, herbal remedies can alter a broader range of biological pathways and processes to treat depression and prevent the negative consequences of antidepressant medications[56].

Wang *et al*[57] conducted research using molecular docking and network pharmacology to investigate the mechanism of Sinisan Formula (SNSF) in treating depression. SNSF is a widely recognized TCM formula that comprises four herbs: *Licorice* (Gancao), *Aurantii Fructus Immaturus* (Zhishi), *Paeoniae Radix Alba* (Shaoyao), and *Bupleurum chinense* (Chaihu). In the SNSF database, 91 active compounds are associated with 112 targets associated with depression. Additionally, SNSF might modulate its antidepressant properties by managing the signaling pathway of neuroactive ligand-receptor, GABA, dopamine, and 5-hydroxytryptamine relationships[58]. Numerous TCM remedies have been reported for their potential

efficacy in managing depression.

Decoction of Baihe Dihuang

Baihe, scientifically known as *Lilium brownii var. Viridulum* possesses properties associated with nourishing Yin and moisturizing the lungs, clearing the heart, and promoting mental tranquillity. Dihuang, scientifically known as *Rehmannia glutinosa,* contains therapeutic properties such as heat-clearing and blood-cooling actions, Yin nourishment, and fluid generation[59]. The Baihe Dihuang decoction is commonly administered to address cognitive instability, absent-mindedness, agitation, and depressive symptoms. Additionally, brain-derived neurotrophic factor (BDNF), Akt, TrkB-dependent phosphoinositide 3-kinase (PI3K), and mTOR1 synapses may be involved in the critical signal pathways of Baihe Dihuang Decoction in the multi-target treatment of depression and GABAergic and glutamatergic synapses[60]. Lu *et al*[61] discovered that Baihe Dihuang decoction decreased monoamine oxidase activity in an animal model of chronic mild unpredictable stress, which prevented the breakdown of monoamine neurotransmitters like norepinephrine, 5-hydroxytryptamine, and dopamine and exhibited antidepressant effects.

Hypericum monogynum L. (Jin Si Tao)

Jin Si Tao, known as *Hypericum monogynum* L., is an herbal plant. It is known for its various beneficial effects, including relaxing the liver and alleviating depression, as well as clearing heat and dampness. Additionally, it has properties that can reduce swelling and relieve pain[62]. Sadeghi *et al*[63] reported that when comparing the two treatments' effects on patients with mild and moderate depression, they discovered that *Hypericum perforatum* was more effective than antidepressants. Hypericin and several flavonoids were identified as the primary antidepressant components in Jin Si Tao (*Hypericum monogynum* L.), according to an analysis of clinical data by Gao *et al*[64]. These compounds may potentially participate in the treatment of depression by exerting inhibitory effects on 5-hydroxytryptamine, monoamine oxidase B, and monoamine oxidase A. Additionally, they control gene expression in the hypothalamus and the hypothalamic-adrenal axis.

Bupleurum (Chaihu) and Paeonia lactiflora (Shaoyao)

The fundamental combination of Shaoyao (*Paeonia lactiflora*) and Chaihu (*Bupleurum*) is the basis for prescriptions such as Xiao Chaihu decoction, Sini powder, and Xiaoyao powder. Chaihu (*Bupleurum*) relieves fever, soothes the liver, relieves depression, and lifts Yang Qi, whereas Shaoyao (*Paeonia lactiflora*) nourishes blood, collects Yin, soothes the liver, relieves pain, calms the liver, and suppresses Yang[65]. Xie *et al*[66] study the effects of Shaoyao (*Paeonia lactiflora*) and Chaihu (*Bupleurum*) with antidepressants on their chemical, target, and mechanism using network pharmacology and a persistent and unpredictable mild stress rat paradigm. Similarly, Shen and colleagues found that Shaoyao (*Paeonia lactiflora*) and Chaihu (*Bupleurum*) regulate arginine and proline metabolism and are antidepressants. Frequent and unstable mild stress develops in a rat depression model[67].

Moreover, Proteomics was employed to study Chaihu (*Bupleurum*) and Shaoyao's antidepressant mechanisms. The findings imply that this system is linked to neuroprotection, oxidative stress, immunological response, and neuroplasticity[68]. Wu *et al*[69] discovered in a rat swimming experiment that *Bupleurum's* primary antidepressant, saikosaponin, has the same effect on depression as fluoxetine on high-dose saikosaponin. The efficiency of Shaoyao (*Paeonia lactiflora*) extract in depression animal models suggests that paeoniflorin or a combination of the two may be the potent antidepressant component.

Chaihu Shugan San

Chaihu Shugan San can effectively treat depression by releasing liber-qi stagnation from rage or distress, according to the Chinese medical classic "Jingyue Quanshu". The Chinese herb blends Chaihu Shugan San contains seven distinct herbs: *Glycyrrhiza uralensis Fisch* (GanCao), *Citrus aurantium L* (ZhiKe), *Cyperus rotundus L* (XiangFu), *Ligusticum chuanxiong Hort.* (ChuanXiong), *Paeonia lactiflora Pall*. (BaiShao), *Citrus reticulata Blanco* (ChenPi), *Bupleurum chinense DC* (CaiHu)[70]. Its antidepressant action may affect several targets and pathways, including potential control of 110 DEPs and neurotransmitter transmission cycles, according to a proteomics study. Kaempferol, luteolin, and quercetin were likely active substances, and the PI3K/AKT pathway could be a potential mechanism. A rat model of depression is utilized by Fan *et al* [71] to determine whether Chaihu-Shugan-San, a TCM mixture, can reduce symptoms. The findings indicated that Chaihu-Shugan-San has a therapeutic impact on an *in vivo* PSD model and can control microglia polarization *via* activating the JAK/STAT3-GSK3-PTEN/Akt pathway, suggesting that it works by reducing neuroinflammation.

Kai-Xin-San

Kai-Xin-San (KXS) is frequently used to treat depression. Each formula is a concoction of various herbs that are said to function concurrently on a variety of pathogenic targets. Their formulation and dose depend on the symptoms of certain people. When treating complex disorders like depression, TCM's holistic, multidrug, and multi-target approach meshes well with the therapeutic ethos of systems medicine[72]. A meta-analysis used sucrose consumption and 5-HT levels in a depression model to evaluate KXS's depression treatment efficacy. Eight sucrose preference trials included 70 mice; four 5-HT studies contained 38 animals. The KXS trial demonstrated positive results in depression treatment[73]. The information provided by Chen *et al*[74] leads one to believe that miR-1281 targets ADCY1 and DVL1. The results indicate a novel link between miR-1281 and depression based on the *in vivo* identification of miRNA expression profiles. KXS can also stimulate the signal transduction pathways for Wnt/-catenin and cAMP/PKA/ERK/CREB, according to *in vitro* tests. MiR-1281, which targets ADCY1 and DVL1, is down-regulated during this activation, resulting in the protection of neuronal cells.

Capsules of Shuganjeyu

The Chinese drug regulatory body approved *Shuganjieyu*, a combination of *Acanthopanax senticosus* (Rupr. [Maxim.], CiWuJia), and GuanYeLianQiao *Hypericum perforatum* L. (GuanYeLianQiao) as the first CHM for the treatment of depression[75]. The potential antidepressant efficacy of Shuganjieyu capsules is believed to be attributed to an elevation in phosphorylation levels of the cyclic adenosine monophosphate response element binding protein and an upregulation of BDNF expression in the medial prefrontal cortex and hippocampal CA3 region of a rat model exhibiting depressive symptoms[76]. Further studies are needed to explore the potential antidepressant effects of Shuganjeyu capsules.

Dai-Kenchu-To

A three-herb decoction called Dai-Kenchu-To (DKT) is used to treat GI issues. DKT therapy has been shown to stop bacterial translocation in rats under extreme stress and maintain microbiome diversity. Additionally, studies have shown that DKT improves small intestine motility in dogs and rats, avoids postoperative intestinal blockage in rats, and enhances intestinal blood flow in rodents. It is abundantly apparent from these studies that DKT dramatically improves GI tract functionality and can completely prevent the danger of GI tract dysregulation in the pathophysiology of depression[77].

Xiao Yao-san

Since ancient times, China has employed Xiao Yao San (XYS) decoction and its variations as the most popular CHM for treating depression. The mixture is prepared using a combination of eight different herbs, such as *Glycyrrhiza uralensis Fisch* (GanCao), *Mentha haplocalyx Briq* (BoHe), and *Pori cocos [Schw.] Wolf* (FuLing), *Zingiber officinale Rosc.* (GanJiang), *Angelica sinensis [Oliv.] Diel* (DangGui), rhizome of *Atractylodes macrocephala Koidz* (BaiZhu), *Bupleurum chinense D* (ChaiHu), *Paeonia lactiflora Pal* (BaiShao). It is essential to highlight that *Angelica sinensis* is commonly utilized in this formula to enhance blood quality and facilitate blood circulation[78]. Zeng *et al*[79] reviewed 26 randomized controlled trials on XYS for depression. The results showed that XYS and antidepressants were equally effective. The results above provide evidence of combining XYS with antidepressant medication instead of using antidepressants alone. Both XYS and antidepressants have fewer side effects than either alone. It is essential to approach this finding with caution in light of the potential influence of publication bias and the limitations in the quality of clinical research.

According to preclinical research, XYS improves BDNF expression in the hippocampus, regulates the hypothalamic-pituitary-adrenal (HPA) axis, increases 5-HT levels in the cerebral cortex and hippocampus, and lowers cytokine levels in the blood when administered to stress-induced animal models. Researching TCM formulas presents several challenges. The relationships between distinct herbals' constituent parts can make understanding their action methods more difficult. Future research on TCM formulae can use this study's technique and process as a model[80]. In addition to the mentioned herbal therapies, other traditional botanical remedies have also been reported for their potential effectiveness in alleviating depression symptoms (Table 1).

TCM HERBAL ANTIDEPRESSANTS: THE MOLECULAR MECHANISM OF THEIR ACTION

The HPA axis

Stress triggers the activation of the HPA axis, often accompanied by elevated levels of glucocorticoids. These increased glucocorticoid levels can negatively affect neurons' survival and the generation of new neurons, ultimately leading to depressive symptoms. It is crucial to emphasize that interactions involving neurological, hormonal, or inflammatory signals occur between the central nervous system (CNS) and the HPA axis, immunological system, or endocrine system. These systems form a network that plays a crucial role in the mechanism of action of antidepressants. For example, antidepressants that work on monoamines can counteract the heightened activity of the HPA axis induced by stress. Additionally, they can diminish the secretion of pro-inflammatory cytokines from activated microglia, thereby mitigating alterations in inflammatory pathways[81].

In a similar vein, agents that are capable of reducing inflammatory effects have been found to exhibit antidepressant-like activity in animal models. This activity is believed to result from the interaction between the central nervous and immune systems[82]. These include glucocorticoid receptor antagonists, vasopressin receptor antagonists, and antagonists of the receptors for corticotropin-releasing hormone. By preventing the actions of specific receptors, these substances may be effective antidepressants. This would help to stop the adverse effects of hormone secretions caused by the overactivity of the HPA axis due to stress[83].

Ginsenoside Rg3, a protopanaxadiol ginsenoside from *Panax ginseng* C. A. Mey., has been shown to have anxiolytic and antidepressant-like effects in animal models of chronic unpredictable stress by dehyperactivating the HPA axis by lowering corticotropin-releasing hormone, corticosterone, and adrenocorticotropic hormone[84]. Research has shown that this molecule exhibits anti-inflammatory effects by decreasing the levels of inflammatory cytokines in mice stimulated with lipopolysaccharide (LPS).

Transmission of glutamates

The development of fast-acting antidepressants has recently focused on inhibiting glutamate transmission. Enhancing glutamate transmission with drugs like NMDA receptor channel blockers and its positive allosteric modulators and acetylcholine muscarinic (AChM) receptor antagonists can quickly repair stress-induced synaptic defects by increasing BDNF release and synapse function[85]. As the first rapid-acting antidepressant, ketamine [the S (+) enantiomer of the

Table 1 List of additional herbal treatments that exhibit antidepressant-like effects

Ref.	Herbs	Herbal constituents	Administration dosage	Models	Mechanism of action
Terpenes and phenylpropanoids					
Alotaibi *et al*[78], 2022	*Illicium dunnianum* Tutch.	Macranthol	10, 20, 40 mg/kg, p.o.	CUMS mice	BDNF
Dai *et al*[56], 2022	*Magnolia officinalis* Rehd et Wils.	Honokiol	2, 4, 8 mg/kg, i.g.	CUMS mice	The HPA axis/BDNF
Zhao *et al*[40], 2023	*Psoralea corylifolia* Linn.	Bakuchiol analogs	0.03-333 μM	Tr-CHO cells	Monoamine
Zeng *et al*[79], 2021	*Hemsleya amabilis* Diels	Cucurbitacin IIa	2.5, 5 mg/kg, i.p	CUMS mice	BDNF
Chen *et al*[80], 2023	*Crocus sativus* L.	Crocin	12.5, 25, 50 mg/kg, i.p.	Rats	BDNF
Adam *et al*[116], 2023	*Perilla frutescens* (L.) Britt.	Rosmarinic acid	5 and 10 mg/kg, i.p.	CUS Rats	BDNF
Carbohydrates					
Bildziukevich *et al*[117], 2023	*Acanthopanax* Miq.	Chiisanoside	2.5 and 5 mg/kg, i.p	LPS-induced mice	BDNF
Salehi *et al*[118], 2023	*Aconitum carmichaelii* Debeaux	Fuzi polysaccharide 1	50, 100 mg/kg, i.p.	Mice	BDNF
Li *et al*[119], 2022	*Morinda officinalis* How	Oligosaccharide	5, 10, 125, 500 mM	CORT-induced PC12	The HPA axis
Alkaloids					
Salehi *et al*[118], 2023	*Aconitum carmichaelii* Debeaux	Total alkaloid	10, 30 mg/kg, i.g.	Ovariectomized mice	BDNF
Ali *et al*[120], 2023	*Stephania tetrandra* S. Moore	Tetrandrine	10, 20, 40 mg/kg, i.g.	CUMS Rats	Monoamine/BDNF
Shayganfard[121], 2023	*Berberis aristata* Linn.	Berberine Chloride	5, 10, 20 mg/kg, i.p	Male albino mice	Monoamine
Sun *et al*[122], 2023	*Scutellaria baicalensis* Georgi	Baicalein	1, 2, 4 mg/kg, i.p.	CUMS mice	BDNF
Flavonoids					
Yu *et al*[123], 2022	*Pueraria lobate* (Willd.) Ohwi	Puerarin	60 and 120 mg/kg, i.g	CUS Rats	Monoamine/the HPA axis
Yu *et al*[123], 2022	*Pueraria lobate* (Willd.) Ohwi	Pueraria isoflavone	10 and 100 mg/kg	Ovariectomy mice	BDNF
Wang *et al*[124], 2021	*Apocynum venetum* L.	Flavonoid Extract	25, 50, 100 mg/ml	CORT-induced PC12	BDNF
Mu and Ma[125], 2022	*Gastrodia elata* Bl.	Gastrodin	50, 100, 200 mg/kg, i.p.	CUS Rats	BDNF
Glycosides					
Nagakura[126], 2022	*Gentiana lutea* L.	Gentiopicroside	50, 100, 200 mg/kg, i.g.	Reserpine-induced mice	Glutamate transmission
Yin *et al*[127], 2023	*Paeonia lactiflora* Pall.	Total glycosides	160 mg/kg, p.o.	CORT-induced rats	BDNF
Sánchez *et al*[128], 2023	*Rhodiola rosea* L.	Salidroside	20, 40 mg/kg, p.o	Behavioral despair rats	The HPA axis/BDNF
Saponins					
Liu *et al*[129], 2023	*Anemarrhena asphodeloides* Bunge	YY-23	20 mg/kg, i.g.	CMS mice	Glutamate transmission
Zhuang *et al*[58], 2023	*Bupleurum chinense* DC.	Saikosaponin D	0.75 and 1.50 mg/kg, i.g.	CUMS rats	The HPA axis
Yoon *et al*[130], 2023	*Panax ginseng* C.A. Mey.	Ginsenoside Rg1	40 mg/kg, i.p.	CUMS rats	BDNF
Tian *et al*[131], 2023	*Anemarrhena asphodeloides* Bunge	Sarsasapogenin	12.5, 25, 50 mg/kg, p.o.	CUMS mice	Monoamine

CUMS: Chronic unpredictable mild stress; BDNF: Brain-derived neurotrophic factor; HPX: Hypothalamic-pituitary-adrenal; CUS: Chronic unpredictable stress; CORT: Corticosterone.

NMDA receptor antagonist ketamine] was licensed in 2019 to treat severe depression. *Datura stramonium L. Hyoscyamus niger L*., and *Datura metel L*., are all members of the *Solanaceae Juss* family of plants containing Scopolamine. This significant tropane alkaloid can easily penetrate the brain-blood barrier and block AChM1 receptors in the CNS[86]. The latest study has shown that an antidepressant effect of Scopolamine can be seen after just one dose (25 g/kg) in rats. A rise in glutamate transmission and synapse function in the spine is thought to be responsible for its antidepressant effects. This effect is mediated by blocking the AChM1 receptor on GABA interneurons[87].

Chaihu-jia-Longgu-Muli-tang and Yueju pills are two herbal formulae lately showing rapid-acting antidepressant-like actions in animal models, joining Scopolamine. Depression-like behaviors were reduced, BDNF expression was enhanced in the hippocampus, AktmTOR signaling was activated in the prefrontal cortex[88], and NR1 expression was downregulated when a dose of Yueju pill ethanol extracts (3 g/kg) was administered. The administration of Chaihu-jia-Longgu-Muli-tang at a dose of 2.1 g/kg has been found to have a quick-acting antidepressant effect in mice undergoing olfactory bulbectomy[89]. This effect is achieved by activating the AktmTOR signaling pathway and restoring the balance between AMPA and NMDA receptors in the prefrontal cortex. Additionally, these substances have been shown to produce antidepressant effects in chronic animal models *via* monoaminergic systems and the HPA axis[90].

Transmissions of monoamine

According to monoamine speculation, depression is produced by impaired monoamine neurotransmissions. Inhibiting monoamine reabsorbing transporters improves synaptic cleft monoamine supply and transmissions. Conventional antidepressants primarily target monoamine reuptake transporters for serotonin (5-HT) and norepinephrine (NE)[91]. Likewise, other proteins, such as postsynaptic receptors and metabolic enzymes, also contribute to monoamine transmissions. The monoamine-based inhibitors increase 5-HT or NE transmission, altering firing activity in the locus coeruleus or dorsal raphe nucleus in various ways[92]. The efficacy of *Polygala tenuifolia Willd* (Yuanzhi) has been demonstrated in clinical practice, showing expectorant, tonic, tranquilizer, and antipsychotic effects. This plant is commonly included in empirical formulations used to treat depression, including KXS. Before Yuanzhi-1, a triterpenoid saponin derived from *Polygala tenuifolia Willd*., was recently discovered to be a triple monoamine reuptake inhibitor with high efficacy, its mode of action in the treatment of depression had not been thoroughly characterized[93].

In addition, various derivatives of Yuanzhi-1 have demonstrated antidepressant-like actions in animal behavioral models compared to those of the standard antidepressant duloxetine[94]. Ibogaine, a hallucinogenic alkaloid found in *Tabernanthe iboga*, is one example of how it has been empirically utilized to treat depression. Serotonin and dopamine transporters have been demonstrated to be inhibited by ibogaine. However, unlike other transporter ligands, ibogaine inhibits these transporters non-competitively. It appears to bind to the extracellular surface of a conformation of the transporter that faces the cytoplasm[95] (Figure 2).

Neurotrophins

Lack of BDNF affects depression's pathogenesis. Stress-induced downregulation of CREB mRNA level, as well as its phosphorylation, BDNF expression, and neurogenesis, can be restored by antidepressant medicines[96]. This suggests that an agent capable of directly stimulating the BDNF signaling cascade could be an effective antidepressant. The potential drug targets in the BDNF cascade should aim to enhance CREB activity and BDNF expression[97]. Additionally, they should activate the BDNF receptor TrkB or stimulate post-receptor signaling cascades like Ras-Raf-ERK, PI3K-Akt, and PLCγ[98]. Furthermore, Ginsenoside Rg5 has been found to have antidepressant-like effects. It reverses the reduction in hippocampal BDNF expression and TrkB phosphorylation caused by chronic social defeat[99].

Inflammatory pathway

TCM can potentially prevent the onset of depression during its early stages effectively. There is a connection between immune dysregulation, particularly concerning inflammatory processes and depressive symptoms[100]. Specifically, elevated levels of pro-inflammatory cytokines in the bloodstream and the resulting activation of microglia in the brain contribute to neurobiological alterations associated with depression. These changes ultimately give rise to the behavioral symptoms characteristic of depression. In contrast to the administration of endotoxins like LPS, chronic unpredictable mild stress treatment increases the immune system's pro-inflammatory or neuroinflammatory response in the blood and brain by activating the IDO pathway or pro-inflammatory cytokines[101]. It is vital to note that the deregulation of the peripheral immune system significantly influences the etiology of depression. Through increased blood-brain barrier permeation, peripheral cytokines can be effectively carried into the CNS, decreasing serotonin neurotransmission and stimulating the axis of HPA[102].

Bupleurum chinense is a plant frequently utilized for its medicinal properties in treating inflammation and infectious diseases. The compound Saikosaponin-D is a triterpenoid saponin extracted from *Bupleurum chinense*. It possesses various pharmacological effects, including anti-inflammatory and antidepressant activity[96]. Recently, icariin, a prenylated flavonoid extracted from *Epimedium brevicornu Maxim*, has been shown to reduce inflammation and oxidative stress-induced brain damage by inhibiting NF-κB signaling and the NLRP3-inflammasome/caspase-1/IL-1β axis in the hippocampus. Trans-cinnamaldehyde, a bioactive component of *Cinnamomum cassia Presl*, inhibits microglia activation and reduces stress-induced inflammation. In animal studies, trans-cinnamaldehyde has antidepressant effects by inactivating the NF-κB/NLRP3 inflammasome pathway[103].

Therefore, it is possible to utilize anti-inflammatory agents to proactively prevent depression by addressing immune dysregulation before it leads to neurobiological alterations in the brain. However, no CHM components have been shown to affect cytokine receptors specifically[104]. Recently, the anti-inflammatory activity of a key drug category known as "Qing-Re-Yao" has been investigated. These medicines are specifically designed to treat syndromes related to inflam-

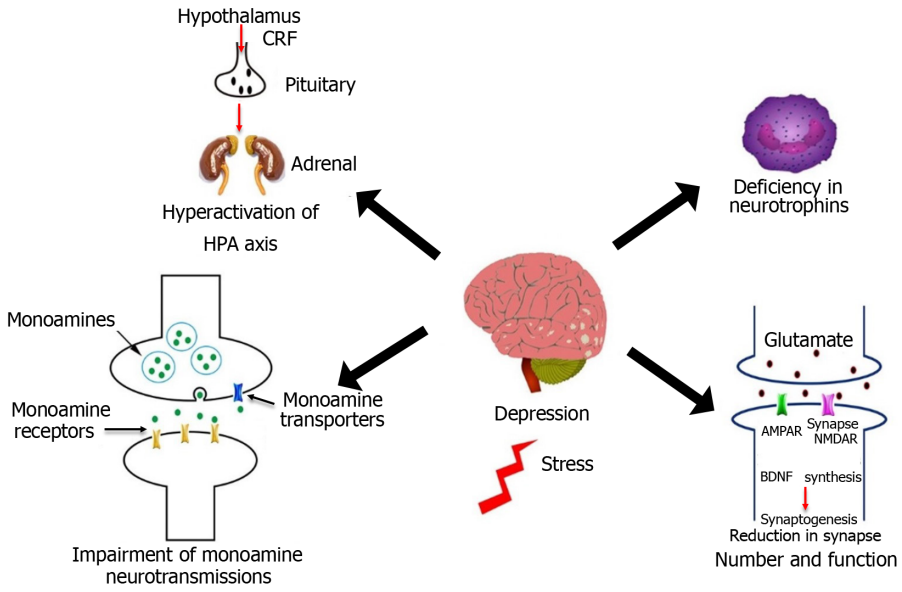

Figure 2 Combine pathways-induced depression. Changes in different parts of the central nervous system (CNS) cause depression. Herbal antidepressants may work on the following pathophysiological systems in the CNS: Neurotrophins, monoamine, the hypothalamic-pituitary-adrenal (HPA) axis, neurotransmissions, and the amount and function of synapses. When these processes don't work right, there are more cases of depression. In the same way, efforts to find antidepressants that work on these systems have led to many pharmaceutical targets, such as improving monoaminergic transmissions, dehyperactivating the HPA axis, raising the expression of neurotrophic factors, and improving glutamatergic transmissions. CNS: Central nervous system; CRGF: Colorectal Carcinoma-Related Growth Factor; HPA: Hypothalamic-pituitary-adrenal. Citation: Li C, Huang J, Cheng YC, Zhang YW. Traditional Chinese Medicine in Depression Treatment: From Molecules to Systems. *Front Pharmacol* 2020; 11: 586. Copyright © 2019 Frontiers Media S.A. All rights reserved (Supplementary material)[113].

mation. TCM formulations designed to alleviate depressed symptoms caused by inflammation typically use at least one herb in this particular category. The study's findings revealed that a significant % of herbs, precisely 93%, demonstrated anti-inflammatory properties through at least one underlying mechanism. Moreover, approximately 68% of the herbs exhibited anti-inflammatory activity through two or more mechanisms[105].

SAFETY AND SIDE EFFECTS OF TCM

Ensuring the safety of TCM interventions for depression is a critical consideration in pursuing holistic well-being. TCM encompasses diverse modalities, including acupuncture, herbal remedies, and mind-body practices, each with its safety profile and potential side effects[106]. Acupuncture is considered safe when trained and licensed practitioners adhere to rigorous hygiene and sterilization standards. However, minor side effects like mild bruising, bleeding, or temporary discomfort at the needle insertion sites may occur. These effects are typically transient and self-limiting.

Moreover, individuals seeking acupuncture for depression should ensure that practitioners are qualified and adhere to established safety guidelines[107]. Herbal medicine is another prominent facet of TCM that requires careful consideration. It is essential to recognize that herbs can carry risks, particularly in interactions with conventional medications or the potential for allergic reactions. The safety of TCM herbal prescriptions hinges on the expertise of the practitioner in selecting appropriate herbs and dosages tailored to the individual's needs[108].

Open communication about medical history, existing medications, and any adverse reactions is essential to mitigate potential risks and ensure a safe and effective treatment approach. TCM herbal formulations, often comprising a combination of various plant materials, minerals, and animal products, may lead to adverse reactions or interactions when used alongside conventional pharmaceuticals[109]. For example, certain TCM herbs could affect the metabolism of medications, leading to altered drug concentrations in the body. Moreover, there may be the potential for allergic reactions or sensitivities to specific herbal components[110].

CHALLENGES

TCM therapy for depression is accompanied by challenges that warrant careful consideration. Firstly, the lack of standardized treatment protocols challenges ensuring consistent and replicable outcomes. TCM therapies, which often involve a combination of herbal formulations, acupuncture techniques, and other practices, can vary in their application and dosages. Additionally, the lack of large-scale, high-quality clinical trials on TCM therapy for depression makes it difficult for healthcare practitioners to safely offer these therapies as part of comprehensive treatment strategies[111]. Secondly, the potential for herb-drug interactions is a concern that requires close attention. Many TCM herbal remedies consist of complex formulations derived from multiple ingredients, raising the possibility of interactions with conven-

tional medications[112]. Furthermore, the cultural gap challenge complicates integrating TCM therapy into mainstream mental health care. Differences in diagnostic paradigms, treatment philosophies, and language barriers can hinder communication and collaboration between TCM practitioners and conventional healthcare providers[113].

The challenge of ensuring quality control and safety in TCM therapies cannot be understated. TCM herbal products, mainly when sourced from unregulated markets, may carry contamination risks or adulteration. Moreover, the lack of standardized outcome measures for assessing the effectiveness of TCM therapy for depression poses a significant limitation[114]. Unlike conventional clinical trials that rely on standardized depression rating scales, TCM interventions may require tailored or alternative measures that capture their unique therapeutic effects[115]. This limitation underscores the need to develop appropriate assessment tools that encompass the holistic nature of TCM therapy and align with its underlying principles.

RECOMMENDATIONS AND FUTURE DIRECTIONS

For healthcare practitioners, patients, and policymakers contemplating TCM as a viable treatment option for depression, a multifaceted approach is essential. Firstly, fostering open and respectful communication between conventional healthcare providers and TCM practitioners is paramount. Collaboration allows for a comprehensive understanding of the patient's health journey, ensuring that TCM interventions align with the overall treatment plan and are well-coordinated with other therapies. Healthcare practitioners should actively educate themselves about TCM principles and practices, enabling them to engage in informed discussions with patients about potential benefits, risks, and interactions. Incorporating TCM into a patient's care requires careful consideration of their medical history, current medications, and individual preferences, focusing on personalized, patient-centered care.

Patients considering TCM for depression should prioritize informed decision-making. Seeking care from qualified TCM practitioners who possess appropriate credentials and experience is crucial. Patients should engage in open dialogues with TCM practitioners and conventional healthcare providers, disclosing all relevant medical information and ongoing treatments. It is crucial to approach TCM interventions with realistic expectations, recognizing that they may complement but not replace conventional therapies. Patients should proactively assess their responses to TCM interventions, providing feedback to TCM and traditional practitioners to ensure a holistic and integrated approach to their mental well-being.

Policymakers play a pivotal role in facilitating the integration of TCM into mental health care systems. Developing guidelines and regulations that uphold safety, efficacy, and ethical standards in TCM practice is imperative. Policymakers should advocate for robust research initiatives to further explore the potential of TCM in depression treatment, fostering evidence-based practice. Creating pathways for interdisciplinary collaboration, training programs, and information sharing among healthcare practitioners from TCM and conventional backgrounds can foster a cohesive, patient-centric approach to mental health care. By embracing these recommendations, harmonious integration of TCM into mainstream mental health care can be achieved, offering patients a broader spectrum of choices for managing depression and promoting holistic well-being.

CONCLUSION

This comprehensive review underscores the multifaceted landscape of TCM as a potential therapeutic avenue in alleviating depression. An extensive analysis of diverse studies and empirical evidence shows that TCM offers a holistic and integrative approach that extends beyond the conventional boundaries of Western Medicine. The synthesis of findings reveals promising outcomes in applying TCM modalities such as acupuncture, herbal medicine, mind-body practices, and dietary interventions for managing depressive symptoms. The collective body of research reviewed here indicates that TCM therapies have the potential to contribute positively to depression management, promoting emotional well-being and enhancing overall quality of life. However, the intricate interplay of cultural, scientific, and practical factors requires careful navigation. Exploring TCM's efficacy in depression treatment is an ongoing endeavor that demands continued interdisciplinary collaboration, rigorous clinical investigation, and enhanced dialogue between TCM practitioners, conventional healthcare providers, patients, and policymakers. While our preclinical research has provided promising insights into the transformative impact of TCM on depression, we acknowledge the necessity for rigorous clinical investigations to strengthen the validity of these preliminary results. As part of our ongoing research, we are actively planning and initiating controlled clinical trials that will meticulously assess the efficacy of TCM interventions using validated clinometric scales. These trials aim to provide a robust foundation for translating our preclinical findings into clinically relevant outcomes, ultimately contributing to the broader understanding of TCM in treating depression. While this review underscores the potential of TCM, it is essential to acknowledge the existing limitations, such as the heterogeneity of study designs, the need for more robust clinical trials, and the necessity for standardized outcome measures. These limitations emphasize the imperative for further research that employs rigorous methodologies to elucidate TCM's mechanisms of action, optimal application, and long-term effects. As we move forward, harnessing the collective wisdom of both Eastern and Western traditions holds the promise of a more holistic and patient-centered approach to depression management that bridges cultural divides and embraces the strengths of diverse therapeutic paradigms. Ultimately, the efficacy of TCM in alleviating depression remains a dynamic field ripe for exploration, collaboration, and the advancement of patient care in mental health.

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FOOTNOTES

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REVIEW

Neurosurgical and pharmacological management of dystonia

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Abstract

Dystonia characterizes a group of neurological movement disorders characterized by abnormal muscle movements, often with repetitive or sustained contraction resulting in abnormal posturing. Different types of dystonia present based on the affected body regions and play a prominent role in determining the potential efficacy of a given intervention. For most patients afflicted with these disorders, an exact cause is rarely identified, so treatment mainly focuses on symptomatic alleviation. Pharmacological agents, such as oral anticholinergic administration and botulinum toxin injection, play a major role in the initial treatment of patients. In more severe and/or refractory cases, focal areas for neurosurgical intervention are identified and targeted to improve quality of life. Deep brain stimulation (DBS) targets these anatomical locations to minimize dystonia symptoms. Surgical ablation procedures and peripheral denervation surgeries also offer potential treatment to patients who do not respond to DBS. These management options grant providers and patients the ability to weigh the benefits and risks for each individual patient profile. This review article explores these pharmacological and neurosurgical management modalities for dystonia, providing a comprehensive assessment of each of their benefits and shortcomings.

Key Words: Botulinum toxin; Magnetic resonance imaging-guided focused ultrasound; Surgical ablation; Deep brain stimulation; Peripheral denervation surgery; Antipsychotics

Core Tip: Dystonia is a neurological movement disorder affecting different regions of the body with variable responses to current interventions. Pharmacological agents, such as oral anticholinergic and botulinum toxin injection, play a major role in the initial treatment of patients. However severe and/or refractory cases require the identification and targeting of focal areas for neurosurgical intervention. Deep brain stimulation (DBS) targets these anatomical locations to manage symptoms. Surgical ablation procedures and peripheral denervation surgeries also offer potential treatment to patients who do not respond to DBS.

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INTRODUCTION

Dystonia is the third most common movement related disorder, behind Parkinson's and essential tremor[1]. Dystonia is defined by numerous characteristics including age of onset, region of body where symptoms occur, and pattern of occurrence[2]. Clinical manifestations of dystonia vary widely but are often characterized by contracted and slowed movements with associated jerky or rapid movements intermittently occurring[3]. It is estimated that 16.7% of patients will also have an observable tremor[4]. They can occur anywhere in the body and once they occur, they usually do not regress[3].

The incidence of dystonia is commonly debated but has been estimated to affect 16.43 per 100000[5]. The incidence rates rise as the subjects age, with a study showing that there were 743 cases per 100000 in patients over the age of 50[6,7]. Pairing this rate with the additional information that only 33% of the subjects being previously diagnosed suggests that the true prevalence of dystonia is higher than officially reported[6,8]. Dystonia is more commonly reported in patients that regularly partake in skillful, precise movements such as painting or playing golf[9]. Dystonia is also more likely to occur in females[10]. Dystonia is highly linked with sensory dysfunction as well and can present as decreased sensation to light touch and proprioception[11,12]. In certain instances of focal hand dystonia, vibration of the affected arm can actually induce dystonia.

Despite the symptoms being well described, the origin of dystonia disorders is not[13,14]. With that being said, there is mounting evidence that suggests there are specific genes that could potentially play a role in the development of dystonia, which vary with the location and subclassification of dystonia[13,15]. The most common cause of early onset dystonia is a deletion at position 302/303 of TorsinA, although the function of the gene itself is still largely unknown[16]. Additional non-genetic factors, including cigarette smoking and head/neck trauma, play a role in the pathogenesis [17,18]. Thirty percent of Parkinson's patients have dystonia, suggesting there is genetic overlap with the two conditions which are often mistaken for each other[19].

With variable presentation and treatment response based on the affected region of the body, understanding management approaches and their efficacy is crucial in providing patients with dystonia the most suitable treatment options. This review will discuss pharmacological and neurosurgical management options for dystonia, highlighting the benefits and drawbacks of each management approach.

PHARMACOLOGICAL MANAGEMENT

Pharmacological management of dystonia traditionally consists of the use of anticholinergic drugs, baclofen, clonazepam, and other dopamine-related medications[20,21]. This review will also discuss the use of antipsychotics and botulinum toxin (BT) injections.

Anticholinergics

The most common anticholinergic drug used to treat dystonia is trihexyphenidyl[22]. It is a selective muscarinic acetylcholine receptor agonist that blocks cholinergic activity. It can also increase the availability of dopamine which plays a role in the initiation and control of muscle movements. The onset of action is about an hour after when administered orally, with a peak after 2-3 h, while the duration of action is between 6 h to 12 h[23]. Dosage begins at 1 mg per day and is raised until either a dose of 30 mg is achieved or adverse drug responses present[22]. A study on Dyt1 knocking mice (mice with the ΔE-TorsinA mutation which causes DYT1 dystonia) found that trihexyphenidyl can correct dopamine release in the mice indirectly through the use of a nicotinic receptor-dependent pathway[24]. Another study found that 20% of patients reported a favorable response when treated with the drug[25]. Despite the common use of trihexyphenidyl, there is literature that has shown that it may be ineffective in treating certain types of dystonia like cerebral palsy, although it did show promising results in the treatment of others like Costello syndrome[23,26]. Other anticholinergics have also been used such as benztropine, ethopropazine, procyclidine, and biperiden but did not show the same effectiveness as trihexyphenidyl[27].

Baclofen

Baclofen is a GABA-B agonist that binds to the pre-synaptic GABA-B receptors, leading to the hyperpolarization of the motor horn cells and reduction in the reflexes that lead to muscle spasms. Due to its inability to cross the blood-brain barrier, high doses of oral baclofen are required to reach therapeutic effects resulting in a greater possibility of adverse drug reactions such as muscle weakness, nausea, and dizziness. In contrast, intrathecal baclofen can bypass the blood-brain barrier, allowing for its administration at a lower dose. However, it is reserved for patients who experience intolerable adverse effects or fail to respond to the maximum recommended dose of oral baclofen[28]. It was found that the same proportion of patients reported a similar favorable response to baclofen as trihexyphenidyl[25]. It is administered 3 to 4 times per day. Dosage is started at 5 mg and increased by 5 mg per day for 3 d to 5 d until either a favorable effect is achieved or adverse drug reactions present[22].

Clonazepam

Clonazepam is the most commonly used benzodiazepine in the treatment of dystonia[22]. Clonazepam directly impacts the benzodiazepine receptors by impacting the GABAergic transmission in the brain. Administration begins at 0.5 mg and is increased to 1.0 mg to 4.0 mg, divided three times a day. Forty percent of patients reported a favorable response to Clonazepam[25]. Adverse effects include confusion, impaired coordination, depression, and dependence[22].

Dopamine-related medications

Some dystonia, such as dopamine-responsive dystonia, can be responsive to treatment with dopamine-related medications such as levodopa[22]. Levodopa is a precursor to dopamine[29]. Upon oral administration, much of the dose is decarboxylated to dopamine so only a small amount reaches the central nervous system. As a result, it is often prescribed with a dopa-decarboxylase inhibitor, like carbidopa, to reduce its conversion in peripheral tissue and reduce side effects. Administration is usually 100 mg tablets with a 100 mg increase every day up to 1200 mg daily to reach therapeutic effects[22]. There have also been instances in which treatment with levodopa has induced dystonia, specifically in patients with atypicalparkinsonism[30-32]. Slightly over 10% of patients reported favorable responses with levodopa[25].

Clozapine

There have also been several different studies that have utilized clozapine to treat dystonia and associated disorders[33-36]. Clozapine is an antipsychotic that will occupy dopamine D2 receptors and will be displaced after a rise in synaptic dopamine[37]. In one study, Clozapine was administered at 12.5 mg per day and was increased by 25.0 mg per day up to a total of 900.0 mg per day unless adverse drug reactions such as persistent symptomatic orthostatic hypotension or tachycardia presented. Of the five participants in the study, all had reached significant improvement in dystonia presentation by the third week, but only two continued to use the medication following the completion of the study[34]. The use of clozapine is limited due to its side effects and need for additional monitoring.

BT therapy

BT is commonly used for blepharospasm, adult spasticity, headache, and cervical dystonia treatment[38,39]. It is the treatment of choice for those with focal dystonia[40,41]. BT inhibits acetylcholine release in the α-motor neuron[42]. It is injected into muscles and produces a localized peripheral paresis[43]. Therapeutic effects usually manifest within 2 wk and will last for about 3 to 4 months[22]. Adverse effects include dry mouth, neck weakness, dysphagia, and voice changes/hoarseness. Most adverse effects were considered to be mild[41].

Certain types of dystonia had a more favorable response to BT injections. For instance, BT injection benefits lasted significantly longer in patients who used treatment for focal handdystonia[44]. There is also some evidence that BT type A could be affected by changes in the cerebral cortex[45]. In order to administer the toxin, ultrasound can be used. This allows the injector to clearly identify and inject the correct muscle rather than relying on blind injections. It also allows for the accurate administration of the drug to deeper muscles[46]. Unfortunately, there is a possibility of developing antibodies for BT, resulting in the need for more frequent injections[47].

NEUROSURGICAL MANAGEMENT

Neurosurgical management of dystonia is considered in cases that impact quality of life and activities of daily living, typically following a lack of response to pharmacological interventions[48]. Deep brain stimulation (DBS) is the mainstay of treatment, replacing previously common ablative procedures[49-52]. Along with DBS, other surgical procedures include pallidotomy, thalamotomy, and peripheral denervation[48].

DBS

The use of DBS for treatment of dystonia has been validated by several cohort studies, demonstrating significant improvements of symptoms from 3 months to up to 7 years[50,51,53,54]. Several target sites have been investigated for DBS treatment of dystonia, including the ventral intermediate nucleus of the thalamus, the subthalamic nucleus, and the globus pallidus pars interna (Figure 1)[55-59], with the primary target site being the globus pallidus pars interna[60-63]. Electrodes are implanted at sites relevant to muscle contractility such as the subthalamic nucleus and globus pallidus pars interna, exhibiting stimulatory effects on axon terminals, in turn, inducing neurotransmitter release[64]. This external source of activation stimulates the malfunctioning regions to produce their normal functions. The frequency of

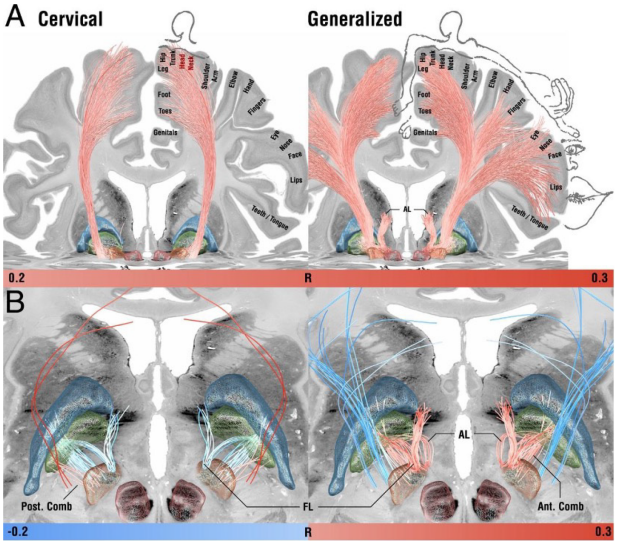

Figure 1 Tracts associated with optimal outcome for patients with cervical (left) and generalized (right) dystonia[85]**.** A: On a broader scale (slightly lower threshold), modulation of corticofugal tracts from the somatomotor head and neck region was associated with optimal outcomes in cervical dystonia, while tracts from the whole somatotopical domain were associated with generalized dystonia; B: On a localized level (slightly higher threshold), in cervical dystonia, striatopallidofugal tracts of the posterior comb system were associated with optimal outcomes. In contrast, fibers from the fasciculus lenticularis were negatively associated. In generalized dystonia, both pallidothalamic bundles (ansa and fasciculus lenticularis) were associated with optimal outcomes, as was a more anterior portion of the comb system; C: Across the cervical and generalized cohorts, the degree of how fittingly the identified networks were modulated by each patient's E-field correlated with clinical improvements. While these correlation analyses are of circular nature, a permutation statistic (bottom) showed superior model fits for unpermuted *vs* permuted improvement values. Citation: Horn A, Reich MM, Ewert S, Li N, Al-Fatly B, Lange F, Roothans J, Oxenford S, Horn I, Paschen S, Runge J, Wodarg F, Witt K, Nickl RC, Wittstock M, Schneider GH, Mahlknecht P, Poewe W, Eisner W, Helmers AK, Matthies C, Krauss JK, Deuschl G, Volkmann J, Kühn AA. Optimal deep brain stimulation sites and networks for cervical vs. generalized dystonia. *Proc Natl Acad Sci U S A* 2022; 119: e2114985119. Copyright© The Authors 2022. Published by National Academy of Sciences of the United States (Supplementary material).

stimulation has the potential to alter both the rate and pattern of firing of the neurons in the area surrounding the electrode[65]. Adverse effects of treatment may include incoordination, postural instability, rigidity, dysphonia, dysarthria, paresthesia, perioral tingling, and micrographia. These effects are mediated by way of inadvertent targeting of neighboring structures around the globus pallidus pars interna, including the optic tract ventrally, internal capsule medially, and hypothalamus superiorly[66,67]. Other hardware related adverse events include infection of the skin or implant, malfunction related to internal pulse generator erosion of failure, and electrode or extension wire damage[68]. Battery life is an additional challenge of DBS, presenting with the most difficulty in pediatric cases where many battery changes are required over the course of their life and thus a higher risk of surgical complications is apparent[69,70]. The advent of rechargeable devices has somewhat alleviated this problem in both pediatric and adult populations, demonstrating lower complication rates and higher patient satisfaction[71,72]. DBS of the subthalamic nucleus and globus pallidus pars interna has also demonstrated favorable outcomes in patients who previously underwent pallidotomy but continued to present with progressive symptoms[73,74].

In pediatric patients, benefits following DBS have been reported 5 or more years following implantation[69]. The anatomical changes depending on the age of the child also pose difficulties as the anatomical structure is growing rapidly and altering the surgical target site. Intraoperative visualization of brain anatomy and site targeting require significantly increased precision to successfully localize DBS electrodes[75,76]. Furthermore, children may lack the appropriate endurance and communication abilities needed to determine the therapeutic window during the postoperative stimulation sessions[77]. Therefore, reaching stable stimulation settings may pose a greater limitation in the pediatric population. Pre- and post-operative measures of dystonic qualities must also be considered when assessing the validity of DBS. The Burke-Fahn-Marsden Dystonia Rating Scale, a universally applied scale for dystonia used for both adult and pediatric patients, may not properly delineate the difference between dystonic movements and movements of healthy, developing children[78,79]. For the pediatric patient specifically, multidimensional assessment of disability prior to and after neurosurgical intervention is necessary beyond the level of mere impairment-focused quantitative measures[80]. Long-term adverse effects of DBS should also be examined, as the duration of implantation increases with decreasing age. An additional consideration in the pediatric patient is requiring more battery changes for non-rechargeable devices over their lifetime, potentially increasing the complication rates[70]. In a 6-month pediatric follow-up study, 10.3% of implant participants experienced surgical site infections, most of them necessitating total removal of the device[81]. Another study with a longer 4.6-year average follow-up duration yielded similar results, with 9.7% of the cohort undergoing postoperative surgical intervention for wound infections[82]. More comprehensive reviews targeting the pediatric population should be implemented to assist physicians and caregivers in making informed decisions on utilizing DBS.

Electrode types for DBS are platinum-iridium wires and connectors made of nickel alloy encased in a sheath of polyurethane[83]. Electrode configurations vary based on contact number, shape, and spacing. Precise stimulation control is achieved with small contact spacing whereas a greater range of neural targets can be achieved with increased contact spacing. Stimulation types include unipolar, bipolar, interleaving, multiple level, and directional. Unipolar stimulation

describes current movement directed either from the battery to the contact or from the contact to the battery. Bipolar stimulation describes current movement between at least one cathode and one anode contact. Interleaving stimulation describes a system of interchanging settings and multiple level stimulation allows for stimulation of several neuronal targets along the electrodes trajectory. Directional stimulation allows for current shaping. Directional stimulation has specifically demonstrated treatment efficacy and reduced adverse effects[84]. Because of the use of radially segmented contacts, directional stimulation enables horizontal plane movement of the stimulation field. In the context of directional stimulation, increasing contact numbers and current amplitudes must be weighed against their impact on treatment feasibility in the context of programming and hindrances on stimulation field shaping.

Surgical ablation

Ablation approaches include radiofrequency ablation, stereotactic radiosurgery, and magnetic resonance imaging (MRI)-guided focused ultrasound (MRgFUS)[48,85-88]. The main concern for these procedures is the irreversible nature and potential damage of neighboring structures near the site of ablation. With the main target site being the thalamus, the surgical depth required carries an increased risk for damaging surrounding structures such as those of the optic tract, internal capsule, and hypothalamus[89]. Despite these concerns, recent studies emphasize the non-invasive nature of MRgFUS, highlighting the precision allowing for ablation of target tissue without damage to surrounding structures[90-93]. MRgFUS uses focused ultrasound waves to generate heat at the target area, resulting in coagulative necrosis which non-invasively destroys the targeted tissue. This is guided with high-resolution MRI imaging to allow clinicians to precisely visualize the target tissue and surrounding structures. The continuous monitoring and adjustment during the procedure maximizes safety and accuracy. Additionally, the development of dysarthria is an important, potentially irreversible side effect that may occur with bilateral ablation, most likely attributable to ventrolateral thalamic damage[52,94,95]. With the advent of DBS, surgical ablation may still be indicated in cases where patients are not eligible for DBS, such as limited access to postoperative programming, previous hardware complications, or previous infections[48]. In such cases, evaluation of the benefits and drawbacks of different surgical ablation techniques is required.

MRgFUS is a common option for surgical ablation, allowing for preoperative region mapping, non-invasive administration, and attenuation of damage to neighboring structures[96,97]. However, gait disturbances, paresthesias, and limb dysmetria are considerable side effects associated with this procedure, often due to the primary lesion itself or to perilesional edema[98-100]. MRgFUS may be the preferred technique for surgical ablation as more transient and less severe adverse effects have been reported compared with radiofrequency ablation[86,101,102]. For radiofrequency ablation, electrode placement requires craniotomy or a small burr hole[103,104]. However, recent trials have demonstrated safe bilateral lesioning with this technique[104]. Additionally, the capacity for region mapping prior to the procedure gives radiofrequency ablation an upper hand over stereotactic radiosurgery in preoperative surgical preparation. Although stereotactic radiosurgery provides a non-invasive alternative, radiation induced neurotoxicity is an additional accompanying drawback of the procedure[105-107]. MRgFUS coalesces both the region mapping abilities of radiofrequency ablations and decreased adverse effect profile of the stereotactic technique, placing it at the forefront of therapeutic options for patients with dystonia[108]. A pilot study investigated the efficacy of MRgFUS thalamotomy of the ventro-oral nucleus of the thalamus in 10 patients with focal hand dystonia (Figure 2). They reported significantly improved symptoms and only one serious adverse event (suicide attempt) related to previously concealed attempts and depression, in addition to mild dysarthria in one patient at 12 months (Figure 3). The study sample included professional musicians, writers, and dart-related dystonia. Researchers utilized three scales for quantifying patient clinical improvement: Writer's Cramp Rating Scale, Tubiana Musician's Dystonia Scale, and Arm Dystonia Disability Scale. All three scales demonstrated statistically significant improvement 12 months after treatment. These findings are critical in suggesting the potential benefits of MRgFUS utilization in patients with dystonia, underpinning its clinical efficacy and safety profile.

Thalamotomy constitutes the main surgical ablation procedure for dystonia and has been evaluated in many controlled studies[109]. Small lesions of the thalamus appear reliable and even provide less risk of infection in comparison to DBS, the primary treatment for focal dystonia. Thalamotomy also provides permanent effects and is a more financially achievable technique than DBS. Pallidotomy has not been evaluated in any controlled studies for dystonia but has demonstrated efficacy in a number of case series[52,88,94]. Irreversible side effects remain a potential complication for any type of ablation procedure[109]. Because ablations for dystonia involve the severing of efferent nerve tracts including the pallidothalamic tract and ventral intermediate nucleus, absolute precision is required to mitigate the risk of dysphagia, dysesthesia, and local muscle atrophy can be a result of the procedure[110]. Besides the ventro-oral nucleus, other common sites of thalamotomy include the ventral intermediate nucleus and the globus pallidus pars interna.

Peripheral denervation surgery

The use of peripheral denervation surgery has demonstrated efficacy for treating cervical dystonia in several case series [111-114]. Peripheral denervation is a selective surgery that resects and avulses the specific nerves innervating the muscles responsible for dystonia. Short electrical stimulations are then used to identify other small nerve branches that could be supplementing dystonia symptoms. This is all done with respect to the accessory nerve to avoid post-operative shoulder weakness[111]. Targeted muscles are based on the dominant subtype contributing to symptoms and include muscles of the posterior neck and the sternocleidomastoid muscle[115-117]. Since it is an invasive option, it is typically implemented after conservative measures of treatment have proven ineffective or inappropriate. Additionally, the practice of peripheral denervation has been available for longer than other surgical management options but clinical preference remains unestablished, with one review of 18 studies including both DBS and peripheral denervation use suggesting a current lack of identification of patient subpopulations benefiting more from either approach[118]. Adverse effects of peripheral denervation include dysphagia and return of symptoms following denervation[112].

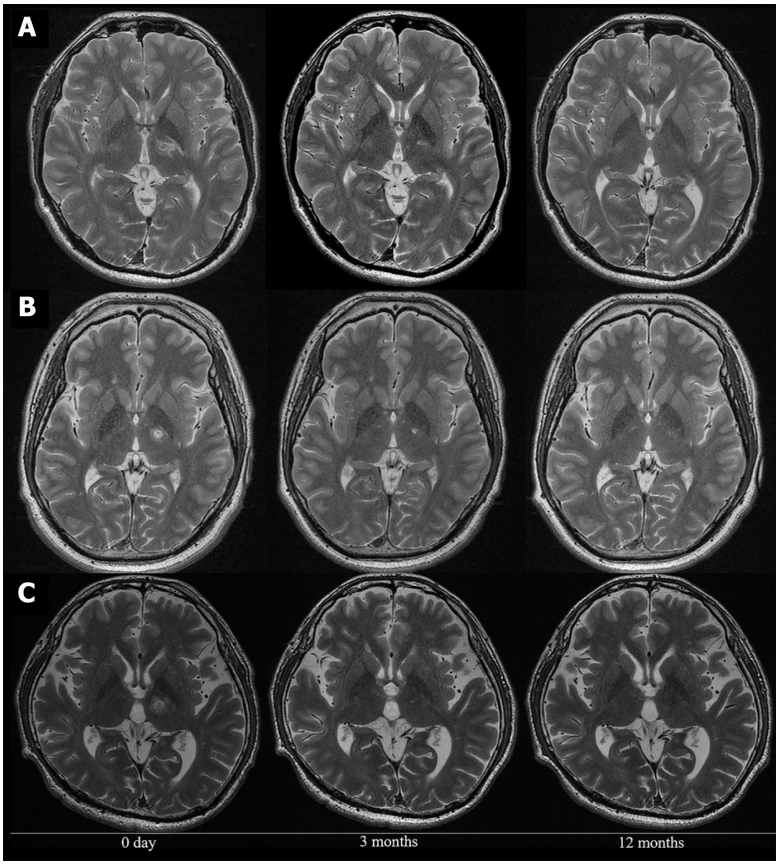

Figure 2 Representative magnetic resonance images obtained before and after treatment[86]**.** A and B: The lesion unexpectedly encroached on the posterior limb of the internal capsule (case 4: A; case 7: B); C: The precise lesion on the intended target. Citation: Horisawa S, Yamaguchi T, Abe K, Hori H, Fukui A, Iijima M, Sumi M, Hodotsuka K, Konishi Y, Kawamata T, Taira T. Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Focal Hand Dystonia: A Pilot Study. *Mov Disord* 2021; 36: 1955-1959. Copyright© The Authors 2021. Published by Movement Disorders published by John Wiley & Sons, Inc. (Supplementary material).

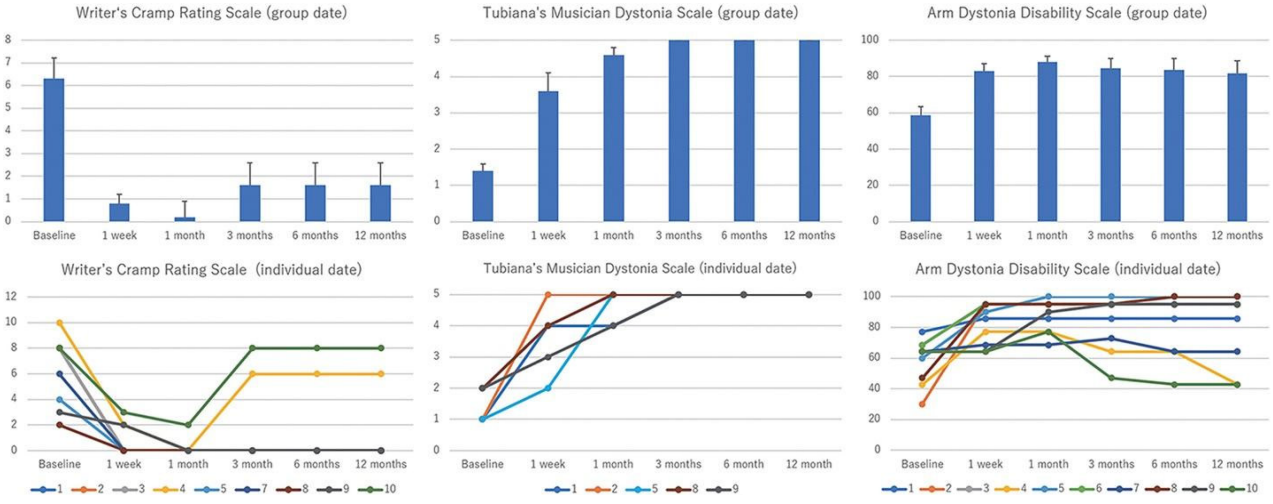

Figure 3 Changes in primary and secondary clinical endpoints during the study period[86]**.** Primary clinical endpoints were the scores of the Writer's Cramp Rating Scale (WCRS; ranging from 0 to 30, with higher scores indicating greater severity) and Tubiana Musician's Dystonia Scale (TMDS; ranging from 1 to 5, with lower scores indicating greater severity), which evaluate dystonia severity. Secondary clinical endpoint was the score of the Arm Dystonia Disability Scale (ADDS; ranging from 0% to 100%, with lower scores indicating greater disability) to evaluate dystonia disability. Significant improvements were observed in the WCRS, TMDS, and ADDS scores throughout the study period in group data (upper row). Individual data are shown in the lower row. Citation: Horisawa S, Yamaguchi T, Abe K, Hori H, Fukui A, Iijima M, Sumi M, Hodotsuka K, Konishi Y, Kawamata T, Taira T. Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Focal Hand Dystonia: A Pilot Study. *Mov Disord* 2021; 36: 1955-1959. Copyright© The Authors 2021. Published by Movement Disorders published by John Wiley & Sons, Inc. (Supplementary material).

CONCLUSION

The current management options for patients with dystonia aim to optimally minimize the motor effects of dystonia on afflicted patients. While the exact etiology is unclear in most cases, potential interventions lie in surgical and pharmacological symptom alleviation. Advancements in precise neurosurgical procedures such as DBS have allowed for better long-term patient outcomes. For different types of dystonia, specific brain regions, such as the output efferent fibers of the globus pallidus pars interna and subthalamic nucleus, have been identified for optimal targeting. Previously used ablative surgeries have also improved through the advent of radiofrequency, stereotaxis, and ultrasound. Even with the use of state-of-the-art technologies, adverse effects remain a significant consideration when weighing these interventions. As a result, the use of pharmacological agents to modulate the aversive effects of dystonia on patient life is prevalent. Careful analysis of the etiology, associated symptoms, and potential side effects should be undertaken before beginning any individual medication. Continued research in the hopes of further symptom alleviation and cause identification is needed to better control the clinical presentation of dystonia and provide patients with more diverse, robust options to consider in their treatment.

FOOTNOTES

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MINIREVIEWS

Physiotherapy for patients with depression: Recent research progress

Hui-Ling Liu, Jing Sun, Shi-Feng Meng, Ning Sun

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Abstract

Depression, a common mental illness, seriously affects the health of individuals and has deleterious effects on society. The prevention and treatment of depression has drawn the attention of many researchers and has become an important social issue. The treatment strategies for depression include drugs, psychotherapy, and physiotherapy. Drug therapy is ineffective in some patients and psychotherapy has treatment limitations. As a reliable adjuvant therapy, physiotherapy compensates for the shortcomings of drug and psychotherapy and effectively reduces the disease recurrence rate. Physiotherapy is more scientific and rigorous, its methods are diverse, and to a certain extent, provides more choices for the treatment of depression. Physiotherapy can relieve symptoms in many ways, such as by improving the levels of neurobiochemical molecules, inhibiting the inflammatory response, regulating the neuroendocrine system, and increasing neuroplasticity. Physiotherapy has biological effects similar to those of antidepressants and may produce a superimposed impact when combined with other treatments. This article summarizes the findings on the use of physiotherapy to treat patients with depression over the past five years. It also discusses several methods of physiotherapy for treating depression from the aspects of clinical effect, mechanism of action, and disadvantages, thereby serving as a reference for the in-depth development of physiotherapy research.

Key Words: Depression; Physiotherapy; Non-pharmacological; Rehabilitation therapy; Recent advances

Core Tip: Depression is a complex mental illness where a patient may exhibit a continuous, long-term low mood (a central feature). Psychotherapy and drug therapy are the most common treatments for depression; however, they have limitations. Physiotherapy is typically used to supplement or replace these therapies. In this study, the literature published in recent years was searched to identify the latest progress in physiotherapy for the treatment of depression and to provide empirical support for improving the cure rate and reducing the recurrence rate of the illness as much as possible.

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INTRODUCTION

The incidence of depression has increased in recent years. Approximately 5% of adults worldwide suffer from depression [1], which has become a global health crisis and is the second largest health killer after cancer in humans. Depression gravely affects normal learning, work, and social activities. It has many manifestations and various pathophysiological mechanisms, including neuroplasticity and inflammation, which can result in diverse symptom patterns. However, no experts have clearly defined the causes of depression. People in different stages of depression exhibit different symptoms. The main signs are low mood, loss of interest and pleasure in things which were normally enjoyable, decreased attention, a low sense of self-worth and self-acquisition, a feeling of foreboding, suicidal ideation, and suicide[2]. Depression can increase the risk of cardiovascular disease, stroke, diabetes, and obesity, and can lead to suicide due to the inability to bear the pain of the illness. Depression is related to morphological and functional changes in different regions of the brain such as the frontal and parietal cortices, the hippocampus, and the thalamus or striatum[3]. These changes represent the basis for the cognitive and behavioral disorders observed in this pathology. For example, changes in the gray matter of the striatum are associated with suicidal tendencies, and dysfunction of the prefrontal cortex-amygdala-hippocampus circuit may be related to the visceral structure of the nerve, resulting in abnormal fear conditioning[4,5]. In traditional treatment methods, doctors often use psychotherapy and drug therapy to regulate the patient's condition. Although this can improve symptoms of depression and anxiety, some patients experience a slow onset of the effects of medication. Long-term use of antidepressants is prone to causing adverse reactions (such as gastrointestinal discomfort), and users can easily relapse after drug withdrawal. This article reviews the literature on physiotherapy for depression over the past five years and discusses commonly used physical interventions to explore their value in the clinical treatment of patients with depression. We hope that this article will serve as a reference for improving the cure rate and reducing the recurrence rate of depression. Figure 1 shows the several types of physiotherapies introduced in this article.

LITERATURE SOURCE

We collected and summarized the latest advancements in new technologies and parameters in the field of physiotherapy for depression. We used electronic and manual searches to retrieve articles on the physiotherapy of patients with depression in the PubMed database over the past five years (from 2018 to 2023). Electronic search terms included "depression", "non-pharmacological therapy", "electroconvulsive therapy", "repetitive transcranial magnetic stimulation", and "deep brain stimulation". The literature that required manual searching was a list of references that emerged from the PubMed search process. We jointly negotiated to resolve or request third-party help when we disagreed about the literature retrieval and screening processes. Due to language limitations, we only included articles published in English.

ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy (ECT) was first used more than 80 years ago and is an established medical practice[6]. It uses electrical means for physiotherapy; that is, through the qualitative discharge of the patient's brain, the patient experiences a transient loss of consciousness to achieve the therapeutic effect. Generally, 8-12 instances of electricity are applied in one course of ECT at a frequency of 2-3 times per week. ECT can compensate for the shortcomings of traditional drug therapy to a certain extent such that many patients with a poor drug response also have the opportunity to recover.

The specific operational steps are as follows: First, two electrodes are placed on the bilateral temporal sides of the head, and then a certain amount of current is transmitted to the patient's skull. After energization, the patient experiences brief convulsions and gradually loses consciousness. After these reactions occur, the patient's head is shifted to one side, and the patient's breathing is assisted until spontaneous breathing is restored[7]. Adults can usually tolerate a voltage of 70-130 V for 0.1-0.5 s or a current intensity of 90-120 mA for 1-3 s. Compared to other treatments, ECT is highly effective and is currently the main physical therapy used for depression. ECT is generally regarded as a last resort and is normally

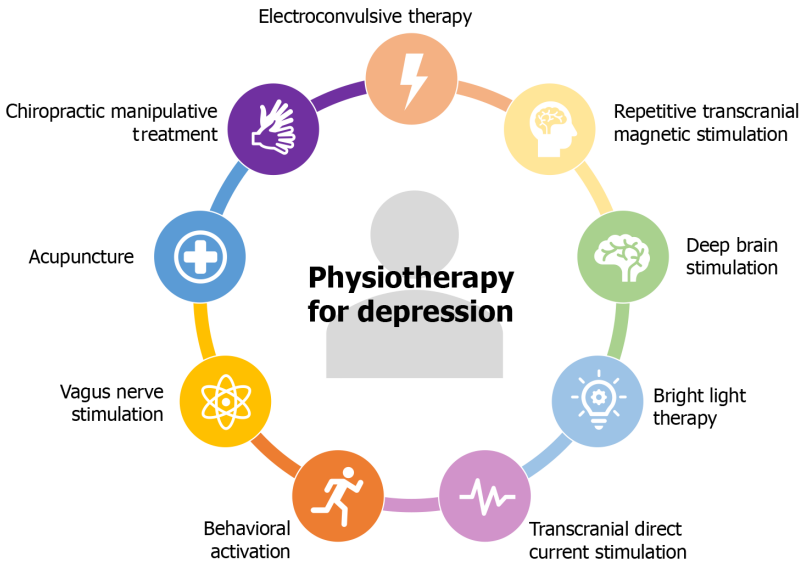

Figure 1 Type of physiotherapy.

used after medication or psychotherapy has failed to produce a positive effect. ECT has excellent cost-effectiveness and should be included in a patient's treatment plan as soon as possible[8]. However, ECT also has certain adverse reactions such as nausea, muscle pain, and headache; however, the duration is short, and the reaction is mild. If required, antiemetic drugs and simple painkillers can be used for symptomatic treatment. In the treatment of epilepsy induction and general anesthesia, ECT is a safe and well-tolerated treatment, and does not increase the risk of dementia or stroke [9]. Thus, the time required for patients to receive ECT can be extended appropriately. To prevent disease recurrence, the frequency of treatment should be gradually reduced when the patient improves, rather than immediately stopping treatment[10]. Table 1 outlines several studies that have used ECT to treat depression[11-15].

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is a non-invasive neuro-electrophysiological technique that interferes with brain function. A coil generates a high magnetic field, which induces a current in a specific area of the brain, depolarizes nerve cells, and changes the state of brain function. It was first discovered and developed by Barker *et al*[16] in 1985 and is used to treat depression[17]. Subsequently, other researchers modified the treatment technology based on problems encountered during the development process. They elaborated a treatment method called repetitive TMS (rTMS) that transmits TMS with repetitive pulses at short intervals[18]. In the past five years, researchers have used rTMS to treat many neurological and mental health conditions to study and evaluate its therapeutic effect[19-21]. rTMS does not require anesthesia, has low requirements for treatment sites (a person can even be treated in an office environment), it avoids the side effects and addiction that drug therapy may bring, and provides a safer treatment option for patients. Studies have shown that frontal lobe function in patients with depression is generally unbalanced. The use of low-frequency TMS (1 Hz, 5 times/week, 15 min/session, 20 times in total) of the right dorsolateral prefrontal cortex (DLPFC) can significantly reduce depression[22]. Between 30% and 50% of patients do not respond adequately to first-line treatment (a combination of drug therapy and psychotherapy). Traditional antidepressants target major neurotransmitters associated with depression such as serotonin, norepinephrine, and dopamine, and the treatment effect often differs markedly among individuals[23]. Although rTMS also has some side effects such as headaches and gastrointestinal discomfort, these may be related to the patient's psychological pressure or physical condition; most side effects are limited in duration and do not lead to long-term adverse outcomes[24]. Despite its disadvantages, rTMS has significant benefits for patients with depression and can be used as an auxiliary physical therapy to treat the illness.

DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is an invasive technique. When the electrode is implanted into the brain, the patient is required to maintain consciousness. The pulse generators are used to stimulate certain nuclei in the deep part of the brain to correct abnormal brain electrical circuits, thereby reducing the patient's neurological symptoms. The first trial of DBS in the treatment of depression by Mayberg *et al*[25] demonstrated its safety and efficacy. In general, when DBS is employed to treat depression, a fixed frequency (130 Hz) and pulse width (90 μs) are used, but two studies have tested the effects of different stimulation parameters[26,27]. In one study, the parameters were set as unipolar stimulation, the amplitude was 4 mA, and the pulse width was 91 μs; a low-frequency stimulation group (20 Hz) and a high-frequency

Table 1 Study of electroconvulsive therapy in the treatment of depression

Ref.	Sample	Results
Abbott *et al*[11], 2021	Of 62 patients with major depressive disorder	The use of 800 mA and 600 mA is more effective in the treatment of depression, but patients with depression in the 800 mA group developed cognitive impairment after treatment
Su *et al*[12], 2023	Of 239 patients with depressive disorder	ECT is more effective in the treatment of patients with severe depression
Gryglewski *et al* [13], 2020	Of 13 patients with major depressive disorder	Twelve patients responded to ECT. The electrode placement position affected the change in the diffusion rate index
Cai *et al*[14], 2023	Of 183 adolescents with depression aged 13-18	After 6 wk of treatment, the ECT group experienced less suicidal ideation and fewer depressive symptoms
Su *et al*[15], 2019	Of 120 patients with major depressive disorder	The electrode-placed on the double frontal, double temporal, and right unilateral sides of the skull-was effective at treating depression

ECT: Electroconvulsive therapy.

stimulation group (120 Hz) were treated[26]. At 6 months, the treatment effect in the low-frequency group (20 Hz) was better than that in the high-frequency group (120 Hz), and at 12 months, high-frequency stimulation was better than low-frequency stimulation. The second study found no difference in the efficacy of DBS with a short pulse width (90 μs) and a long pulse width (210-450 μs)[27]. Transient adverse reactions after DBS such as ghosting, blurring, or dizziness, can be improved by reducing or changing the stimulation parameters. Available evidence suggests that DBS is an effective, safe, and well-tolerated treatment for depression. Open-label DBS studies of different targets have shown that if there is enough time to adjust the initial parameters, the average remission rate of patients with severe drug resistance can reach 50%[28]. DBS has the benefits of a strong recovery and minimal damage to the patient's brain. It does not destroy the patient's brain structure but only conducts the corresponding stimulation treatment on the brain[29]. The stimulation parameters of DBS can be adjusted according to the needs of patients, so it can provide a stable and lasting effect. The effect of drug therapy may be affected by various factors such as drug metabolism, individual differences, and disease progression, resulting in fluctuations in efficacy[30]. There are common problems with DBS treatment, including DBS hardware infection and DBS device battery depletion. No serious adverse events have been observed after proper treatment. Due to its many advantages, professionals have used DBS to treat depression and have achieved certain positive results in the early stages. However, the relevant theoretical research is still in the exploratory stage. Most experimental studies have conducted open-label trials. Problems exist such as a lack of control groups, small sample sizes, and difficulty excluding the placebo effect. With ongoing improvements in technology, it is possible to achieve outstanding value in the treatment of depression.

BRIGHT LIGHT THERAPY

Bright light therapy (BLT), as a physical intervention, is beneficial for treating various depressive disorders, including major and maternal depression; its mechanism may be related to the regulation of abnormal biological clocks, serotonin, and catecholamine systems[31]. Circadian rhythm disorder in patients with depressive disorder is often significantly altered by the sleep-wake cycle and hormone secretion. The effect of light timing on mood may be attained by regulating the phase shift and duration of the nocturnal melatonin secretion rhythm[32,33]. Melatonin induces the expression of Per1 and Per2 through the mediation of downstream protein kinase C to increase the resetting of the suprachiasmatic nucleus clock. Meyerhoff *et al*[34] found that BLT quickly improved symptoms of early insomnia, mental anxiety, drowsiness, and social withdrawal in patients with depressive episodes. Jiang *et al*[35] showed that high-intensity light could effectively improve the State Anxiety Scale scores of patients with subthreshold depression. Symptoms of anxiety are associated with a variety of neurotransmitters, including 5-hydroxytryptamine (5-HT), glutamic acid, norepinephrine, and gamma-aminobutyric acid. Light therapy can adjust the binding potential of 5-HT transporters in the anterior cingulate cortex, thereby regulating 5-HT levels. This is a mechanism by which BLT improves symptoms of anxiety. The focus of conventional drug therapy is to alleviate the patient's depression, while the patient's problems in other aspects are less of a concern. BLT can not only alleviate the symptoms of depression, but also improve the quality of sleep, adjust the sleep cycle, and help patients return to normal sleep patterns. It can also improve overall mental health, reduce anxiety and depression, and help patients to fully recover their health[36,37]. The ideal time to receive intense light therapy is mostly within 10 min after waking, but the treatment cycle is not yet clear; the most common side effects after treatment are headaches and eye problems[38]. Although the effectiveness of phototherapy in the treatment of depression is relatively accurate, the specific optimal configuration of factors - such as light dose (light irradiance, irradiation time, light source distance, and angle), spectrum, and daily exposure time, which affect the clinical efficacy and side effects of phototherapy - has not yet been determined. Further research is required to explore its clinical applications. Table 2 lists several studies that have used BLT therapy[39-42].

Table 2 Related research on bright light therapy

Ref.	Sample	Results
Donmez *et al*[39], 2022	Of 30 cases of pregnant women and postpartum 1-yr patients with depression	BLT effectively alleviated patients' depression
Raymackers *et al*[40], 2019	Of 59 breast cancer patients with depressive symptoms	The efficacy of BLT is better in spring and summer
Rutten *et al*[41], 2019	Of 83 patients with depression and Parkinson's disease	BLT had little impact on the alleviation of patients' depression but effectively improved their sleep status
Chan *et al*[42], 2022	Of 93 patients with non-seasonal depression	The remission rate of BLT therapy in the treatment of non-seasonal depression was relatively high

BLT: Bright light therapy.

TRANSCRANIAL DIRECT CURRENT STIMULATION

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique that transfers a weak direct current to the surface of the cerebral cortex through at least two electrodes, causing changes in the resting membrane potential hyperpolarization or depolarization to regulate cortical excitability and neural network activity[43]. In patients with depression, left DLPFC activity is weakened, blood flow is reduced, metabolism is slowed, and right DLPFC activity is overly enhanced, resulting in an imbalance in DLPFC function on both sides. Hence, the anode of tDCS can be used to stimulate the left DLPFC to improve its excitability, while the cathode can be used to stimulate the right DLPFC to inhibit its excitability, thereby regulating the activity of the brain's emotional loop and alleviating depression[44]. Common adverse reactions such as itching, burning, and headaches are usually mild and do not cause long-term effects[45]. Compared with other neuromodulation methods, tDCS is cost-effective, portable, safe, easy to use, and has considerable therapeutic potential.

VAGUS NERVE STIMULATION

Although vagus nerve stimulation (VNS) was initially widely used to treat epilepsy (and not depression), because it can effectively improve the mood of patients with epilepsy, VNS has been extended to include mental disorders such as depression. In 2005, the Food and Drug Administration in the United States officially approved VNS for the treatment of depression[46]. It has been rapidly developed and has achieved positive outcomes. Through surgical implantation of a VNS device, a bipolar stimulation electrode is configured as the cathode of the proximal lead and the anode of the distal lead. A pain block is established in the distal lead and the action potential is guided to the central nervous system (CNS). Sending electrical pulses to the left cervical vagus nerve stimulates the brainstem pathway of the afferent vagus nerve related to emotional regulation, thereby treating depression[47]. Bottomley *et al*[48] showed that VNS can prolong the duration of antidepressant efficacy and alleviate depressive symptoms in patients. Safety issues related to VNS are minimal. However, the treatment cost of VNS is relatively high, which may pose a certain burden on some patients with limited economic resources. This problem requires consideration.

ACUPUNCTURE

Acupuncture is a promising non-drug treatment for reducing depressive symptoms and can replace drug therapy or complement other therapies to improve outcomes. Manual acupuncture is a traditional technique; a fine metal needle is used to pierce the skin at an acupoint and is then operated by hand through lifting, pricking, and twisting. Compared with drug treatment, acupuncture is affordable and has few side effects[49,50]. From the perspective of traditional Chinese medicine (TCM), the incidence of depression is related to patients' mood and visceral dysfunction. Stimulating specific acupoints of the human body, enhancing the input signal of the motor cortex, and increasing the excitement of the CNS may improve the patient's depressive state and regulate the expression of regulatory T cells, thereby mitigating the immunosuppressive state of depression[51]. Acupuncture treatment usually does not produce drug dependence and resistance, nor does it cause damage to liver and kidney function. Although acupuncture has a certain effect in the treatment of depression, its onset time may vary from person to person. For some patients, multiple treatments may be required to see a significant improvement. Due to the need to stimulate acupuncture points in acupuncture treatment, some patients may be unable to accept this treatment because of fear or discomfort with needles[52].

CHIROPRACTIC MANIPULATIVE TREATMENT

Chiropractic manipulative treatment (CMT) is a massage technique used in TCM; it is combined with the rolling method, lifting, pinching, and point pressing to stimulate the governor vessel and bladder meridians to relax the tendons and dredge the collaterals, thus regulating qi and blood. The symptoms of depression, such as high cortisol, high adrenaline, insomnia, restlessness, and anxiety can be attributed to excessive activity of the sympathetic nervous system[53]. Additionally, dopamine, brain-derived neurotrophic factor, nerve growth factor, and other neuroendocrine factors play a role in the pathophysiology of depression. As a potential treatment, CMT uses spinal finger pressure therapy and VNS to activate the parasympathetic nervous system, reduce the activity of the sympathetic nervous system, synthesize neuroendocrine factors to regulate the autonomic nervous system, and mitigate the symptoms of autonomic nervous imbalance and depression[54].

DISCUSSION

Depression is a common psychiatric disorder characterized by symptoms such as low emotion, a slow thinking response, laziness, and slow movement. It can be accompanied by different degrees of cognitive impairment, which has many negative effects on daily life, work, studying, and social interactions. In severe cases, dangerous behavioral tendencies may occur such as violence and suicide. With the continuous development of bioengineering technology, additional physical therapy approaches are expected to be developed. Thus, professionals in relevant fields must implement reforms and innovations based on existing physical therapies. This article lists several commonly used physical therapies and rehabilitation methods for depression, including ECT, rTMS, and DBS to provide a reference for clinical medical staff when selecting appropriate interventions. Among them, ECT and rTMS have been used for a long time, with more evidence demonstrating a curative effect[55-58]. New physical therapies such as DBS, VNS, and CMT have fewer clinical trials, lack evidence, and need to be further studied[29,53,59].

Currently, ECT is the most efficient form of physical therapy. It can be used to treat patients as soon as possible following an injury or illness. It is extremely safe, has few side effects, and does not lead to dependence on drug treatment[8,9]. Kirov *et al*[6] and Gyger *et al*[7] confirmed the effectiveness and safety of ECT[6,7]. Even so, professionals working with various media and many studies have been skeptical of ECT. Other neuromodulation techniques such as rTMS, DBS, and tDCS have been approved and used; however, there is insufficient evidence to confirm their efficacy. It is gratifying that in the past five years of research, people's attention to physical therapy has gradually increased. Researchers have verified the effectiveness and safety of the above treatment techniques from different perspectives and have explored ways to achieve better efficacy[21,26,27,46]. Most of the time, satisfactory results can be obtained. Occasionally, the outcomes are poor due to various limitations; however, this is a normal phenomenon in research. There are also milder therapies such as BLT. These techniques do not require a high-quality treatment environment and are simple to perform. However, their therapeutic effects are inferior to those of other neuromodulatory approaches. The milder therapies can be used to treat patients with mild depression or as an adjuvant therapy. TCM is widely employed in China. In the treatment of depression using physical methods, the most used approaches are acupuncture and CMT[50,51,54], which are also relatively mild treatments.

CONCLUSION

The current visiting rate of diagnosis of depression is low in China, and the incidence of depression is increasing in the young, which has extremely serious repercussions at the economic and societal levels. There are many types of physical therapies, and the curative effect may differ owing to different stimulation positions, stimulation currents, and time settings. Compared with the conventional treatment of depression, the use of physical therapy for depression does not require surgery, injections, or the use of drugs, therefore the risk of side effects or dependency is very low. Additionally, the adverse effects are usually mild and can be solved by proper treatment. However, some of the milder physical therapy methods have no obvious effect in the short term. This requires the long-term persistence of patients to achieve results, and sometimes needs to be combined with other treatment methods. Based on the existing stage, combined with the advantages of technological development, more scientific clinical research is being conducted to create additional physical therapy methods in line with reality and to reduce the prevalence of depression. Moreover, because the combination of physical therapy with drug therapy and psychotherapy may enhance the antidepressant effect, in addition to designing relevant clinical trials to determine whether a new physical therapy has an antidepressant effect, it is necessary to explore the effectiveness of physical therapy combined with antidepressant drugs as well as that of psychotherapy combined with antidepressants. This should be done to enable the selection of different treatment techniques according to different symptoms to obtain a more obvious curative effect. The occurrence of depression is not caused by a single factor but rather by the comprehensive application of a complex social environment. Hence, attention must be paid to prevention, treatment, popularizing science, choosing from a myriad of treatment methods, improving the clinical cure rate of depression, minimizing the occurrence of suicide, reducing the recurrence rate, and increasing the survival and well-being of patients.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Therapeutic effect and psychological impact of aspirin plus edaravone on patients with cerebral infarction

Tian-Shu Wang, Li-Jun Jing

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Abstract

BACKGROUND

Cerebral infarction (CI) is characterized by a high prevalence, disability, and mortality. Timely or improper treatment greatly affects patient prognosis.

AIM

To explore the drug efficacy of aspirin plus edaravone and to explore their effect on quality of life (QOL), anxiety and depression in CI patients.

METHODS

We retrospectively analyzed the records of 124 CI patients treated between June 2019 and February 2021 who were assigned to an observation group (OG) (combination therapy of aspirin and edaravone, 65 patients) or a control group (CG) (aspirin monotherapy, 59 patients). The therapeutic effects, pre- and posttreatment National Institutes of Health Stroke Scale (NIHSS) scores, activities of daily living, degree of cognitive impairment, protein levels of glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE) and S-100B, occurrence of adverse reactions, and serum high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6 and tumor necrosis factor (TNF)-α were evaluated, detected and compared between the two groups. Finally, posttreatment QOL, anxiety, and depression were assessed by the Medical Outcomes Study 36- Item Short Form Health Survey Scale, Self-rating Depression Scale (SDS), and Self-rating Anxiety Scale (SAS), respectively.

RESULTS

Compared with the CG, the OG had markedly better therapeutic effects, greater improvements in activities of daily living, and better alleviation in cognitive dysfunction after treatment, as well as lower posttreatment NIHSS scores and serum NSE, GFAP, S-100B, hs-CRP, IL-6, and TNF-α levels; the OG was similar to the CG in terms of adverse reactions but was better than the CG in terms of posttreatment QOL; and the OG also had lower SDS and SAS scores than the CG

after treatment.

CONCLUSION
Aspirin plus edaravone had a good curative effect on CI. It can reverse cranial nerve damage in patients, improve neurological function and prognosis, and alleviate inflammation, anxiety, and depression; thus, it is considered safe and worthy of clinical application.

Key Words: Aspirin; Edaravone; Cerebral infarction; Efficacy; Quality of life

Core Tip: Edaravone, a commonly used free radical scavenger in clinical practice, can reduce the concentration of hydroxyl radicals and inhibit lipid peroxidation activity, ultimately achieving effects such as reducing endothelial cell damage and delaying neuronal cell death. It is currently the main drug used for the treatment of acute cerebral infarction. In addition, it can theoretically play a synergistic role with aspirin to improve therapeutic effectiveness, but there are few relevant studies to confirm our view. This study confirmed that aspirin combined with edaravone has more prominent efficacy and other clinical advantages in the treatment of cerebral infarction patients.

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INTRODUCTION

Cerebral infarction (CI), or ischemic stroke, is a localized area of brain tissue necrosis or softening caused by cerebral atherosclerosis, vascular intimal injury or foreign body obstruction resulting in cerebrovascular lumen stenosis and regional cerebral blood oxygen deficiency[1]. The onset of the disease is often acute, with focal neurological signs peaking within minutes to hours, and there is associated functional loss in the associated sites[2]. CI has a high prevalence and high disability and fatality rates and is a serious threat to the health and life safety of elderly people, the main group at which it causes morbidity[3,4]. If not treated in time or if it is handled improperly, various neurological sequelae can occur, which can greatly affect patient prognosis[5].

At present, the clinical treatment principle for CI is to improve blood oxygen circulation in the brain as soon as possible and promote the recovery of neurological function[6]. Apart from thrombolysis, aspirin is the most effective treatment and exerts antiplatelet effects by inhibiting the release of thromboxane A2 and prostaglandins[7]. However, its long-term use was found to cause many adverse reactions, and some patients experienced no improvement or even worsening of CI symptoms after taking it. These findings may be related to the single mechanism of action of aspirin and the complex mechanism of platelet aggregation, leading to the occurrence of drug resistance[8]. Edaravone, an extensively applied free radical scavenger, can reduce the hydroxyl free radical concentration and inhibit lipid peroxidation activity to reduce vascular endothelial cell damage and delay nerve cell death and is currently the main drug used to treat acute CI[9]. In theory, its combined use with aspirin can have synergistic effects and improve therapeutic effects, but there are few related studies.

This study aimed to provide additional clinical evidence for CI treatment by analyzing the efficacy of aspirin plus edaravone therapy in 124 CI patients admitted between June 2019 and February 2021.

MATERIALS AND METHODS

Clinical data

This study retrospectively analyzed the case records of 124 CI patients (64 men and 60 women) treated between June 2019 and February 2021 who were assigned to an observation group (OG) (combination therapy of aspirin and edaravone, 65 patients) or a control group (CG) (aspirin monotherapy, 59 patients). The inclusion criteria were as follows: (1) Met the acute CI diagnostic criteria; (2) Had an initial onset of CI; (3) Had a neurological deficit score (National Institutes of Health Stroke Scale, NIHSS) of 6 or above; (4) Had a blood pressure < 180/100 mmHg; (5) Had not undergone major surgery recently or had a hemorrhagic tendency; and (6) Had undergone neurological factor testing. The exclusion criteria were as follows: (1) Intracranial hemorrhage and no early large-area CI imaging changes; (2) Severe heart, liver, or liver insufficiency; (3) Intracranial hemorrhage within the past 3 months; (4) History of head trauma or myocardial infarction; (5) Severe trauma or active hemorrhage; (6) Platelet count < 100×10^9/L; and (7) Incomplete clinical data.

Treatment method

Both groups of patients were given routine supportive treatment, such as treatments to control blood pressure, maintain blood sugar, prevent infection, and maintain the electrolyte balance, and streptokinase thrombolysis was also performed. During this period, the keeping of real-time clinical records and nursing were performed. On this basis, CG patients were given 100 mg oral aspirin (Sichuan Pacific Pharmaceutical Co., Ltd., H51021475) once daily. Based on the treatments of the CG, OG patients received 30 mg of edaravone (Sinopharm Group Guorui Pharmaceutical Co., Ltd.; H20080056) plus 250 mL of normal saline by intravenous drip twice a day. The drug efficacy obtained in the two groups was compared after two 7-d courses of treatment.

Endpoints

(1) Therapeutic efficacy was evaluated and divided into recovery (the patient's symptoms and signs basically disappeared after treatment, the NIHSS score decreased by ≥ 90% compared with that before treatment, and the degree of disability was 0); marked effectiveness (the patient's symptoms after treatment were significantly relieved, the NIHSS score was reduced by 46% to 90% compared with that before treatment, and the degree of disability was 1% to 2%); effectiveness (the patient's symptoms and signs were relieved to a certain extent after treatment, the NIHSS score was reduced by 18% to 46% compared with that before treatment, and the disability level was 2-3) and ineffective (the symptoms and signs and NIHSS scores of the patients after treatment did not change significantly or even worsened compared with those before treatment). The overall effective rate was the percentage of patients who were categorized as cured, markedly effective, and effective among the total number of patients; (2) Patients were scored by the NIHSS (score range: 0-42)[10] before and after treatment to assess their neurological function in the visual domain, facial paralysis domain, limb movement domain, *etc.* Higher scores indicate more severe neurological deficits; (3) Before and after treatment, patients' activities of daily living (ADL) were assessed with the Barthel index[11] from the dressing, grooming, bathing, bladder function, bowel function, toilet use, transfer (bed or wheelchair), mobility, and stairs domains, with 10 items out of 100. The score is proportional to the number of ADLs; (4) Before and after treatment, the Mini Mental State Evaluation Scale (MMSE, score range: 0-30) was used for cognitive dysfunction assessment, with lower scores suggesting more serious cognitive dysfunction; (5) Fasting venous blood (3 mL) was also drawn before and after treatment, and the samples were centrifuged for biochemical analysis with a Toshiba TBA-2000FR for enzyme-linked immunosorbent assay (ELISA) quantification of neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), and S-100B protein levels; (6) The levels of serum high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6 and tumor necrosis factor (TNF)-α, which are inflammatory factors, were compared before and after treatment *via* an ELISA; (7) Adverse reactions, including skin ecchymosis, melena, nausea, dizziness, and gastric bleeding, were recorded; (8) The Medical Outcomes Study 36-Item Short Form Health Survey Scale[12], which assesses four dimensions of physical function, social function, physiological state, and psychological state, was used to assess quality of life (QOL) after treatment. A higher score suggests a better QOL; And (9) Patients' anxiety and depression before and after treatment were assessed using the Self-rating Anxiety Scale (SAS) and Depression Scale (SDS), respectively. The scores ranged from 0-80 points; higher scores are associated with more severe anxiety and depression.

Statistical analysis

SPSS 19.0 and GraphPad 7 were used for the statistical analysis and visualization of the collected data, respectively. Enumeration data, expressed as percentages, were statistically analyzed with chi-square tests. Intergroup comparisons were conducted with Student's *t* test, and post hoc comparisons were performed with paired *t* tests. This study used $P < 0.05$ as the significance level.

RESULTS

Clinical information

There were no significant differences in sex, age, body mass index, or other clinical information between OG and CG patients ($P > 0.05$; Table 1).

Comparison of therapeutic efficacy

After treatment, 38, 24, and 3 patients were categorized as obtaining markedly effective, effective and ineffective treatment efficacy, respectively, in the OG, while 25, 21 and 13 patients, respectively, received markedly lower therapeutic efficacy in the CG than in the OG (77.97% *vs* 95.38%, $P < 0.05$; Table 2).

Comparison of neurological deficits

The OG and CG had similar pretreatment NIHSS scores ($P > 0.05$); the posttreatment scores decreased in both groups, and the OG exhibited a more prominent decrease than did the CG ($P < 0.05$; Table 3).

Comparison of ADLs

The pretreatment Barthel index scores were also not significantly different between the OG and CG ($P > 0.05$); both groups had improved Barthel index scores after treatment; and the OG had markedly greater scores than the CG ($P < 0.05$; Table 4).

Table 1 General data, *n* (%)

Factors	Observation group (*n* = 65)	Control group (*n* = 59)	χ^2	*P* value
Sex			0.002	0.065
Male	35 (53.85)	32 (54.24)		
Female	30 (46.15)	27 (45.76)		
Age (yr)			0.026	0.871
≤ 65	31 (47.69)	29 (49.15)		
> 65	34 (52.31)	30 (50.85)		
BMI (kg/m^2)			0.039	0.844
≤ 23	32 (49.23)	28 (47.46)		
> 23	33 (50.77)	31 (52.54)		
History of smoking			0.009	0.923
Yes	38 (58.46)	35 (59.32)		
No	27 (41.54)	24 (40.68)		
Diabetes			0.009	0.993
Yes	32 (49.23)	29 (49.15)		
No	33 (50.77)	30 (50.85)		
Hypertension			0.084	0.772
Yes	38 (58.46)	36 (61.02)		
No	27 (41.54)	23 (38.98)		
Drinking habit			0.001	0.981
Yes	42 (64.62)	38 (64.41)		
No	23 (35.38)	21 (35.59)		

BMI: Body mass index.

Table 2 Comparison of therapeutic efficacy, *n* (%)

Curative effect	Observation group (*n* = 65)	Control group (*n* = 59)	χ^2	*P* value
Markedly effective	38 (58.46)	25 (42.37)	-	-
Effective	24 (36.92)	21 (35.59)	-	-
Ineffective	3 (4.62)	13 (22.03)	-	-
Effectiveness of treatment	62 (95.38)	46 (77.97)	8.350	0.004

Table 3 Comparison of neurological deficit scores

Time	Observation group (*n* = 65)	Control group (*n* = 59)	*t*	*P* value
Before treatment	22.18 ± 1.01	22.24 ± 1.13	0.312	0.755
After treatment	11.25 ± 1.05	17.00 ± 1.10	29.772	< 0.001

Comparison of cognitive function

Before treatment, there was little difference in MMSE scores between the OG and CG ($P > 0.05$); the posttreatment MMSE scores increased in both groups, especially in the OG ($P < 0.05$; Table 5).

Comparison of neurological function factor levels

The pretreatment protein levels of NSE, GFAP and S-100B were similar in both groups ($P > 0.05$); after treatment, the

Table 4 Comparison of daily living ability

Time	Observation group (*n* = 65)	Control group (*n* = 59)	*t*	*P* value
Before treatment	52.34 ± 1.53	52.42 ± 1.80	0.267	0.790
After treatment	67.20 ± 1.54	59.37 ± 1.68	27.079	< 0.001

Table 5 Comparison of cognitive function

Time	Observation group (*n* = 65)	Control group (*n* = 59)	*t*	*P* value
Before treatment	21.06 ± 1.07	21.15 ± 1.22	0.438	0.663
After treatment	24.94 ± 1.09	23.20 ± 1.00	9.232	< 0.001

above indicators decreased in both the OG and CG, and the levels were markedly lower in the OG than in the CG (P < 0.05; Figure 1).

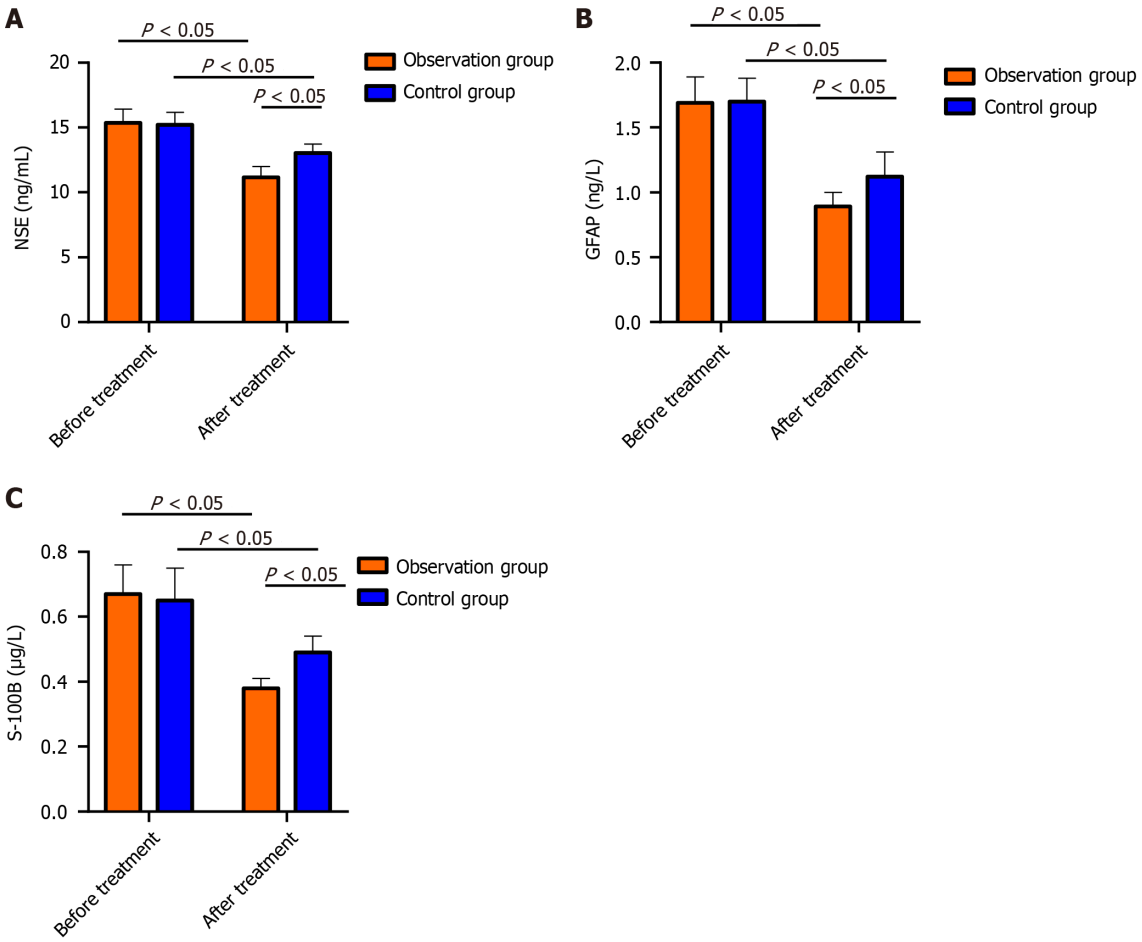

Figure 1 Comparison of neurological function factor levels. A: Comparison of serum neuron-specific enolase; B: Comparison of serum gelatin fibrillary acidic protein; C: Comparison of serum S-100B. NSE: Neuron-specific enolase; GFAP: Gelatin fibrillary acidic protein.

Comparison of serum inflammatory factors

Before treatment, no marked intergroup differences were detected in TNF-α, IL-6, or hs-CRP (P > 0.05); after treatment, the above indices were lower in the OG than in the CG (P < 0.05; Figure 2).

Comparison of the incidence of adverse reactions during treatment

During treatment, a slightly greater total adverse reaction rate was detected in the OG compared with the CG, but without statistical inter-group difference (P > 0.05). Patients in both groups had mild adverse reactions that subsided

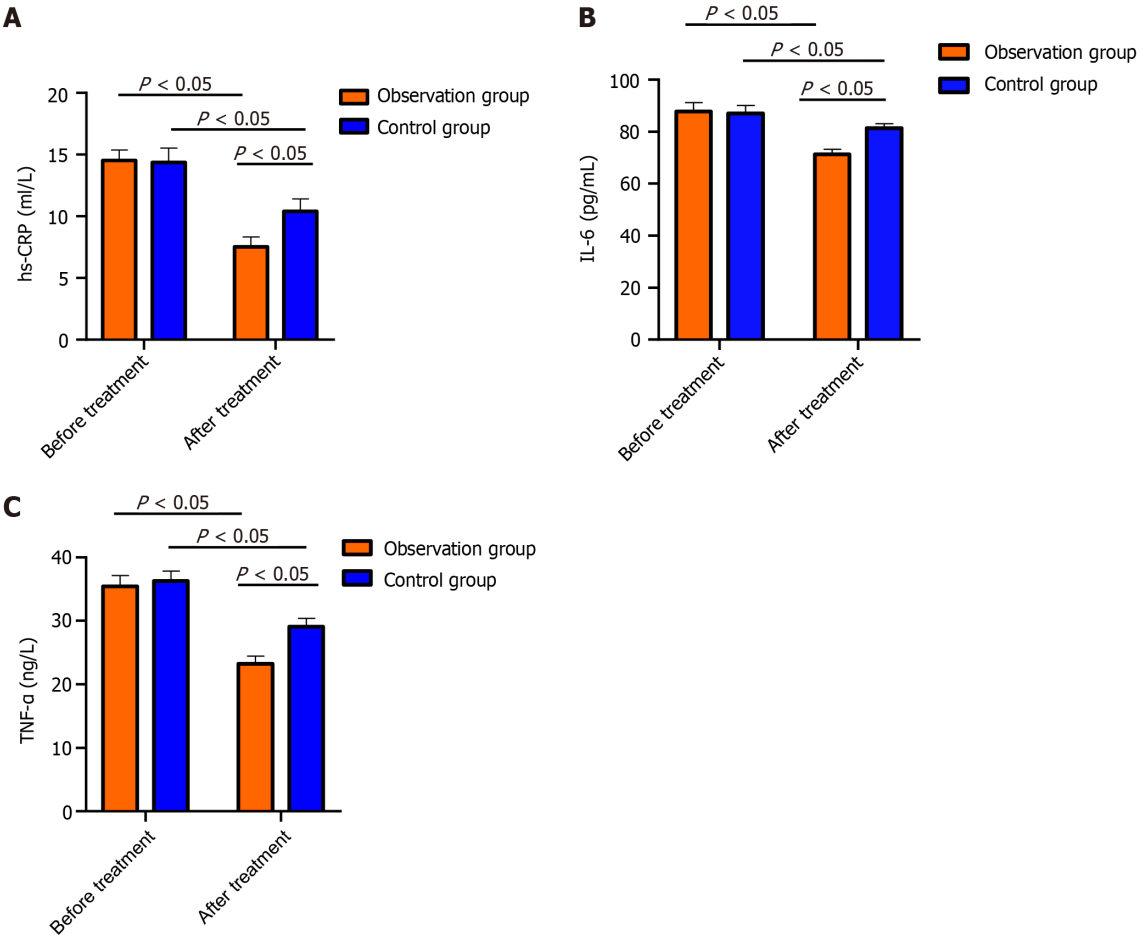

Figure 2 Comparison of serum inflammatory factors. A: Comparison of serum high-sensitivity C-reactive protein; B: Comparison of serum interleukin 6; C: Comparison of serum tumor necrosis factor-α. hs-CRP: High-sensitivity C-reactive protein; IL-6: Interleukin 6; TNF-α: Tumor necrosis factor-α.

naturally without special treatment, which did not affect the follow-up treatment, as shown in Table 6.

Comparison of quality of life after treatment

After treatment, the OG exhibited markedly better physical function, social function, physiological state and psychological state than did the CG ($P < 0.05$; Table 7).

Comparison of anxiety and depression after treatment

Compared with the CG, the OG had significantly lower SDS and SAS scores after treatment ($P < 0.05$; Figure 3).

DISCUSSION

As people's living and eating habits continue to change and the aging population in China increases, the incidence of geriatric diseases has skyrocketed[13]. CI is a frequently occurring clinical disease commonly known as stroke that is affected by different factors and often has a high incidence, morbidity and mortality[14]. CI, characterized by acute onset and rapid disease progression, is believed to be directly associated with hypertension, arrhythmia, diabetes, obesity, *etc.*, with a predilection for middle-aged and elderly individuals (45-70 years old). If the treatment is not timely, intracranial hypertension or severe cerebral edema are very likely to be induced, which will have a great impact on patients' safety [15]. The pathogenesis of CI is complex, and CI exerts a serious impact on patients' vigor and lifespans. Therefore, it is essential to adopt effective treatment measures, such as restoring nerve function and improving blood circulation to the lesion[16].

In clinical practice, antiplatelet agglutination drugs and drugs that lower blood lipid levels in patients are often used to restore the smooth flow of brain microcirculation as soon as possible and actively repair brain cell damage caused by hypoxia[17]. The repair and protection of nerve cells and their systems in the brain can effectively reduce microcirculation disturbance, reduce infarct size, and greatly relieve the symptoms of CI[18]. Aspirin is an anti-platelet aggregation drug and a key drug for CI treatment that can inhibit cyclooxygenase and reduce the conversion of arachidonic acid to thromboxane A2 in platelets, thereby inhibiting platelet aggregation and promoting blood microcirculation[19]. However, aspirin alone can lead to upper gastrointestinal bleeding or liver and kidney damage to a certain extent, which affects its

Table 6 Comparison of adverse reactions during medication, *n* (%)

Adverse reactions	Observation group (*n* = 65)	Control group (*n* = 59)	χ^2	*P* value
Skin ecchymosis	2 (3.08)	1 (1.69)	-	-
Black stool	2 (3.08)	2 (3.39)	-	-
Dizziness	3 (4.62)	1 (1.69)	-	-
Stomach bleeding	2 (3.08)	1 (1.69)	-	-
Total incidence	9 (13.85)	5 (8.47)	0.891	0.345

Table 7 Comparison of the quality of life after treatment

Quality of life	Observation group (*n* = 65)	Control group (*n* = 59)	*t*	*P* value
Body function	62.28 ± 1.39	49.49 ± 1.60	47.625	< 0.001
Social function	65.09 ± 1.44	51.07 ± 1.57	51.868	< 0.001
Physiological state	63.25 ± 1.35	52.00 ± 1.13	50.041	< 0.001
Mental state	65.09 ± 1.38	53.19 ± 1.33	48.788	< 0.001

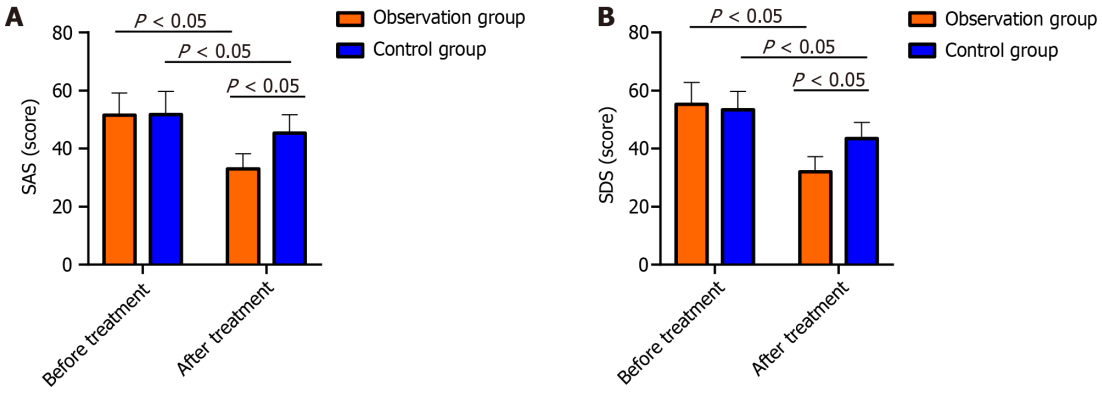

Figure 3 Comparison of anxiety and depression after treatment. A: Comparison of Self-rating Depression Scale scores between groups; B: Comparison of Self-rating Anxiety Scale scores between groups. SAS: Self-rating Anxiety Scale; SDS: Self-rating Depression Scale.

efficacy[20]. Edaravone is a drug with neurotrophic, protective and reparative functions. After edaravone enters brain tissue, it can be embedded in damaged cell membranes and antagonize neurotoxic effects through the inhibition of lipid peroxidation and oxygen free radicals, and excitatory amino acids. Edaravone has unique free radical scavenging effects and can alleviate ischemia-reperfusion, ameliorate lipid peroxidation, and delay neuronal apoptosis, thus alleviating cerebral ischemia symptoms[21]. This study investigated the efficacy of aspirin plus edaravone in treating CI patients. First, we observed that, compared with those of CG patients, the therapeutic efficacy, neurological deficit scores, living ability scores and cognitive function scores of OG patients were markedly greater. This suggested that aspirin plus edaravone could improve drug synergy, improve antiplatelet aggregation while controlling the progression of the patient's disease, and promote the recovery of damaged nerve function. Although aspirin and edaravone both have protective effects on brain tissue, their mechanisms of action are different, and combined application could reduce brain tissue damage through different mechanisms, thereby promoting the recovery of neurological function in patients[22].

NSE is a marker enzyme for nerve cell damage. When the structure of the neuronal cell membrane is damaged after brain tissue ischemia and hypoxia, NSE is released into the blood through the blood-cerebrospinal fluid barrier, causing an increase in NSE[23]. GFAP can induce an inflammatory response in acute anterior circulation CI and aggravate the development of the disease. Damaged brain tissue also leads to an increase in the level of GFAP[24]. S-100B is a marker reflecting brain injury[25]. Deduced posttreatment NSE, GFAP and S-100B protein levels were detected in both groups, with more marked reductions in the OG. Previous studies have shown that edaravone can inhibit the production of arachidonic acid and leukotrienes, relieve cerebral edema and cerebral vasospasm, protect vascular endothelial cell function, enhance cerebral microvssel circulation, and inhibit ischemic cascade reactions, thereby alleviating the symptoms of neurological deficits. In addition, edaravone can also reduce intracellular calcium overload and inhibit the toxic effects of excitatory amino acids, thereby improving nerve loss and exerting neuroprotective effects[26], which explains our observations. Inflammation, which is very important in CI pathogenesis and progression, is positively correlated with disease severity and is an independent etiological factor for assessing patient prognosis and disease

outcomes[27]. Our study revealed that both groups had reduced levels of the inflammatory factors hs-CRP, TNF-α, and IL-6 after treatment, and the inflammatory factors decreased more in the OG than in the control group, suggesting that aspirin plus edaravone could improve the inflammatory response in CI patients and reduce inflammatory factor expression. Subsequently, we comparatively analyzed adverse reactions and QOL. No notable changes in the occurrence of adverse reactions were detected, while the quality of life of OG patients markedly improved after treatment compared with that of CG patients, suggesting that aspirin plus edaravone was safe and did not cause additional adverse reactions. Finally, the evaluation of patients' negative emotions revealed that patients in the OG had significantly lower SAS and SDS than the patients in the CG after treatment, indicating that aspirin plus edaravone is more effective in relieving patients' negative emotions.

CONCLUSION

In conclusion, aspirin plus edaravone is of good curative effect in the treatment of CI patients, which can reverse the cranial nerve damage of patients, enhance their neurological function and prognosis, and relieve inflammation and negative emotions. It is believed to have high safety and the value for clinical popularization. The limitations of this study are as follows: On the one hand, the conclusions needs further validation due to the small sample size. On the other, studies with such positive results are still insufficient and flawed, warranting future prospective, large-sample randomized controlled studies to provide more sufficient evidence.

FOOTNOTES

Author contributions: Wang TS designed the study and wrote the manuscript; Wang TS and Jing LJ performed the data collection, conducted the data analysis and revised the manuscript. All authors approved the final version of the manuscript.

Institutional review board statement: The study was approved by the Institutional review board of First Hospital Affiliated of Zhengzhou University.

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

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

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ORIGINAL ARTICLE

Retrospective Study

Clinical effects of nonconvulsive electrotherapy combined with mindfulness-based stress reduction and changes of serum inflammatory factors in depression

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Abstract

BACKGROUND

Depression is a common and serious psychological condition, which seriously affects individual well-being and functional ability. Traditional treatment methods include drug therapy and psychological counseling; however, these methods have different degrees of side effects and limitations. In recent years, nonconvulsive electrotherapy (NET) has attracted increasing attention as a noninvasive treatment method. However, the clinical efficacy and potential mechanism of NET on depression are still unclear. We hypothesized that NET has a positive clinical effect in the treatment of depression, and may have a regulatory effect on serum inflammatory factors during treatment.

AIM

To assess the effects of NET on depression and analyze changes in serum inflammatory factors.

METHODS

This retrospective study enrolled 140 patients undergoing treatment for depression between May 2017 and June 2022, the observation group that received a combination of mindfulness-based stress reduction (MBSR) and NET treatment (n = 70) and the control group that only received MBSR therapy (n = 70). The clinical effectiveness of the treatment was evaluated by assessing various factors,

including the Hamilton Depression Scale (HAMD)-17, self-rating idea of suicide scale (SSIOS), Pittsburgh Sleep Quality Index (PSQI), and levels of serum inflammatory factors before and after 8 wk of treatment. The quality of life scores between the two groups were compared. Comparisons were made using t and $\chi 2$ tests.

RESULTS

After 8 wk of treatment, the observation group exhibited a 91.43% overall effectiveness rate which was higher than that of the control group which was 74.29% (64 *vs* 52, $\chi 2 = 7.241$; $P < 0.05$). The HAMD, SSIOS, and PSQI scores showed a significant decrease in both groups. Moreover, the observation group had lower scores than the control group (10.37 ± 2.04 *vs* 14.02 ± 2.16, $t = 10.280$; 1.67 ±0.28 *vs* 0.87 ± 0.12, $t = 21.970$; 5.29 ± 1.33 *vs* 7.94 ± 1.35, $t = 11.700$; P both < 0.001). Additionally, there was a notable decrease in the IL-2, IL-1β, and IL-6 in both groups after treatment. Furthermore, the observation group exhibited superior serum inflammatory factors compared to the control group (70.12 ± 10.32 *vs* 102.24 ± 20.21, $t = 11.840$; 19.35 ± 2.46 *vs* 22.27 ± 2.13, $t = 7.508$; 32.25 ± 4.6 *vs* 39.42 ± 4.23, $t = 9.565$; P both < 0.001). Moreover, the observation group exhibited significantly improved quality of life scores compared to the control group (Social function: 19.25 ± 2.76 *vs* 16.23 ± 2.34; Emotions: 18.54 ± 2.83 *vs* 12.28 ± 2.16; Environment: 18.49 ± 2.48 *vs* 16.56 ± 3.44; Physical health: 19.53 ± 2.39 *vs* 16.62 ± 3.46; P both < 0.001) after treatment.

CONCLUSION

MBSR combined with NET effectively alleviates depression, lowers inflammation (IL-2, IL-1β, and IL-6), reduces suicidal thoughts, enhances sleep, and improves the quality of life of individuals with depression.

Key Words: Depression; Nonconvulsive electrotherapy; Mindfulness-based stress reduction; Serum inflammatory factors; Clinical effect; Hamilton Depression Scale

Core Tip: Nonconvulsive electrotherapy (NET) is a promising therapy for depression; however, its clinical effects and underlying mechanisms remain unclear. We conducted a retrospective analysis of data from 140 patients with depression. The control group received mindfulness-based stress reduction (MBSR) therapy, whereas the observation group received a combination of MBSR therapy and NET. Alterations in serum inflammatory factor levels have been observed, suggesting that NET exerts a therapeutic effect by modulating inflammatory levels. This study provides valuable insights for future investigations of the mechanisms underlying the role of NET in depression.

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INTRODUCTION

Depression is a common mental health disorder. Its clinical features mainly include continuous and long-term low mood, reduced interest, and decreased energy. The lifetime prevalence rate is 4.9%. It has a high incidence, repeated attacks, high disability rate, and low cure rate[1]. According to one survey, the prevalence of depression in China is approximately 6.8%. The prevalence of major depressive disorder (MDD) is 3.4%[2]. The annual prevalence of depression is increasing, accompanied by an increase in the complexity of treatment[3]. Studies have predicted that, by 2030, the burden of disease caused by depression will top the global list of mental illnesses[4]. Currently, drugs and psychotherapy are the main treatment methods; however, some limitations remain. Therefore, the identification of additional safe and effective treatment methods has become an important global concern.

Mindfulness-based stress reduction (MBSR) is a type of psychotherapy, which focuses on guiding patients consciously and without judgment to perceive the present to alleviate and release negative emotions, enhance psychological well-being, and facilitate patient rehabilitation. To date, satisfactory results have been achieved in clinical applications[5]. Nonconvulsive electrotherapy (NET) is a novel method to improve nonconvulsive electroconvulsive therapy that aims to stimulate brain neurons without causing systemic convulsions[6]. The stimulation intensity of NET is between those of nonconvulsive electroconvulsive therapy and transcranial magnetic stimulation, and the side effects of the treatment are greatly reduced. Studies have shown that subthreshold stimulation without convulsions can achieve the same therapeutic effect as nonconvulsive electroconvulsive therapy[7]. However, there are relatively few studies from China on the use of NET for the treatment of depression. Accordingly, this study aimed to analyze the clinical effects of NET in the treatment of depression and observe the changes in serum inflammatory factors during treatment to provide a new treatment strategy for the clinical practice and enhance patient outcomes.

MATERIALS AND METHODS

General data

In this study, 140 patients with depression were enrolled from the Guangzhou HuiAi Hospital treatment program between May 2017 and June 2022. Based on the treatment method, the patients were divided into an observation group (n = 70) and a control group (n = 70). Criteria for inclusion were: (1) Individuals who fulfilled the clinical diagnostic criteria for depression according to Chinese Classification and Diagnostic Criteria of Mental Disorders-3; (2) age ≥ 18 years; (3) Hamilton Depression Scale (HAMD)-17 score >17; and (4) only MDD without other chronic diseases that affect mood and inflammatory factors. The exclusion criteria were as follows: (1) Previous history of epilepsy; (2) alcohol dependence or drug abuse; (3) serious physical illness; (4) modified electroconvulsive therapy treatment in the past 2 months; and (5) obvious risk of suicide.

Treatment methods

Both groups of patients were administered 10–20 mg escitalopram oxalate qd and did not take any other anti-anxiety, anti-depression, or other drugs. Based on drug treatment, the control group received MBSR treatment, whereas the observation group received mindfulness decompression combined with NET.

MBSR: One psychological consultant with secondary qualifications was the group leader, two third-level psychological consultants were deputy group leaders, and four experienced nursing staff cooperated. (1) Training time: the training time was 8 wk of centralized training. From the first week of admission, the patients chose to undergo treatment at any time of the day; (2) Training environment: A quiet and undisturbed health education room that met the requirements according to the quality control of MBSR, where the therapist introduced the relevant knowledge of MBSR; and (3) Training method: The patients were divided into seven groups according to the time of admission, with 10 patients per group. Each group underwent collective training for 180 min per session. The first 30 min were taught and explained by the doctor, the next 90 min were self-practice sessions, and the last 30 min were group discussions and summaries. The first week mainly comprised mindfulness eating raisins training; body sensation scanning was performed in the second week; the third week comprised mindfulness awareness breathing training; the fourth week included mindfulness stretching exercises; the fifth week comprised 3 min breathing spaces; the sixth week focused on the mindfulness-awareness idea; the seventh week included autonomous mindfulness awareness and experience, and mindful eating; and in the eighth week, all previous exercises were reviewed, summarized, and shared.

NET: Certain parameters were set to control the intensity of the electrical stimulation. The pulse width was 0.5 ms. Current, frequency, and duration were fixed at 0.9 A, 20 Hz, and 0.5-6.0 s, respectively. The setting of the current study was determined according to the age of the patient and was set to 1/8 of the patient's age. Through a pre-experiment to observe the patient's right lower limb motor convulsions and EEG signals, the current was adjusted to avoid convulsions.

The treatment duration of both groups was 8 wk, and 1-2 times of MBSR were performed every week for 3 h. NET was performed for 30 min, three times a week, with a time interval of less than 2 d.

Observation indicators and evaluation criteria

(1) Comparison of clinical effectiveness and HAMD-17 scores between the groups. Efficacy evaluation: Treatment outcomes for depression were assessed using the HAMD after an 8 wk period[8]. Cured: HAMD score 95%; markedly effective: HAMD score ≥ 8 points, decreased by 70%–95% compared with that before treatment; improvement: HAMD score ≥ 8 points, decreased by 50%–60% compared with that before treatment; ineffective: HAMD score decreased by < 50% compared with that before treatment. The total effective rate was calculated as follows: (cured + markedly effective + improvement)/total number of cases × 100%. A total of 17 items were included in the HAMD scale using a 5-level scoring method of 0 (none) to 4 (extremely severe) points or 0 to 2 points (0: None; 1: Mild-to-moderate; 2: Severe). The severity of the condition increased as the score increased; (2) We used the Pittsburgh Sleep Quality Index (PSQI)[9] to assess the sleep quality of patients before and after treatment. It consisted of 19 self-inspections and five other people's assessments, of which 18 items were categorized into seven factors: Sleep quality, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime functioning. Each factor was scored between 0 to 3 points. '0' refers to no difficulty, '3' refers to very difficult, and 21 points is the highest score. A total score ≥ 7 points indicated a sleep disorder. Sleep quality worsened as the score increased and vice versa; (3) The self-rating idea of suicide scale (SSIOS)[10] was employed to assess suicidal thoughts in both study groups prior to and following the intervention. There were 26 items, including four dimensions: optimism, sleep, despair, and cover-up. Possible answers are 'yes' and 'no.' Higher scores indicate stronger suicidal ideation. If the total score on the scale is greater than or equal to 12 points, an individual can be considered to have suicidal ideation; (4) We compared alterations in serum inflammatory factors before and after therapy between the two groups. We collected 5 mL of fasting venous blood from all patients before and after eight weeks of treatment. The collected blood samples were then analyzed using ELISA kits to determine the serum IL-1β, IL-6, and IL-2 Levels. The detection steps were conducted meticulously following the instructions provided by the manufacturer (Xinxie Biological XinBio); and (5) Patients' quality of life was assessed using the World Health Organization Quality of Life-BREF scale[11], which encompasses various aspects of life, including physiological, social, environmental, and emotional fields. The total score is 100 points, with higher scores indicating a better quality of life.

Statistical methods

SPSS software (version 20.0) was used to analyze descriptive variables, including age, HAMD scores, inflammatory factors, and other measurement data. to the data are presented as mean and standard deviation (mean ± SD) t-tests were conducted to compare the groups. The treatment effect, sex, and other count data are presented as [n (%)], and

Table 1 Comparison of baseline data

Baseline information	Observer group (n = 70)	Control group (n = 70)	χ^2/t value	P value
Sexuality [n (%)]			0.029	0.866
Males	37 (52.86)	36 (51.43)		
Females	33 (47.14)	34 (48.57)		
Age (mean ± SD/yr)	44.62 ± 9.58	46.37 ± 9.42	1.090	0.278
Course of disease (mean ± SD/yr)	4.39 ± 0.44	4.31 ± 0.65	0.853	0.395
HAMD (mean ± SD/score)	30.88 ± 4.16	29.65 ± 3.72	1.844	0.067

HAMD: Hamilton Depression Scale.

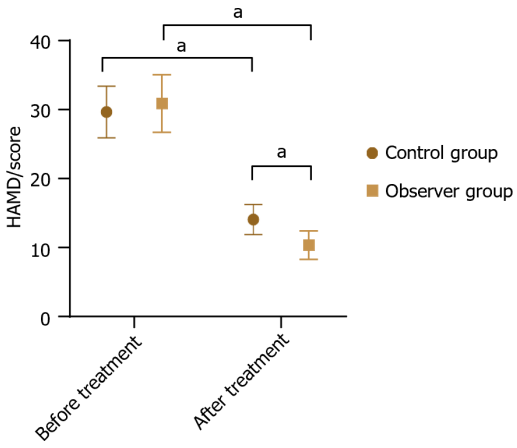

Figure 1 Hamilton Depression Scale score. $^aP < 0.05$. HAMD: Hamilton Depression Scale.

comparisons between groups were performed using the χ^2 test. Asymptotic significance was determined when the P value was < 0.05.

RESULTS

Comparison of baseline data between the two patient groups

There were no significant differences in baseline data between the two groups (all $P > 0.05$; Table 1).

Comparison of HAMD scores before and after treatment

There was no significant difference in HAMD scores between the observation and control groups before treatment (all $P > 0.05$). After treatment, we compared the HAMD scores between the two groups and found that the observation group exhibited lower scores than the control group ($t = 10.280$, $P < 0.05$; Figure 1).

Comparison of the clinical efficacy in the two groups

After undergoing treatment for a period of 8 wk, the observation group achieved a significantly higher effective rate of 91.43% in comparison with the control group's rate of 74.29% ($t = 21.970$, $t = 11.700$; $P < 0.05$; Table 2).

Comparison of SSIOS and PSQI scores in the two groups before and after treatment

Table 3 shows the SSIOS and PSQI scores for both groups which decreased after treatment compared to those before treatment. Additionally, the observation group had significantly lower scores than the control group ($P < 0.05$).

Comparison of serum inflammatory factors

After 8 wk of treatment, IL-2, IL-1β, and IL-6 were noticeably reduced in both groups. Moreover, the observation group displayed enhanced levels of serum inflammatory factors compared to the control group ($t = 11.840$, $t = 7.508$, $t = 9.565$; all $P < 0.05$; Figure 2).

Table 2 Comparison of clinical efficacy between the two groups [*n* (%)]

Groups	Recovery	Effectual	Improvement	Null and void	Total effective rates
Control group (n = 70)	7 (10.00)	14 (20.00)	31 (44.29)	18 (25.71)	52 (74.29)
Observer group (n = 70)	12 (17.14)	20 (28.57)	32 (45.72)	6 (8.57)	64 (91.43)
χ^2/t value	8.390				7.241
P value	0.039				0.007

Table 3 Comparison of self-rating idea of suicide scale and Pittsburgh Sleep Quality Index scores between the two groups before and after treatment (mean ± SD)

Groups	Times	SSIOS/score	PSQI/score
Control group (n = 70)	Before treatment	18.55 ± 4.02	15.83 ± 1.76
	After treatment	0.87 ± 0.12	7.94 ± 1.35
t		36.780	29.760
P value		< 0.001	< 0.001
Observer group (n = 70)	Before treatment	18.88 ± 4.06	15.36 ± 2.54
	After treatment	1.67 ± 0.28[a]	5.29 ± 1.33[a]
t value		35.380	29.390
P value		< 0.001	< 0.001

[a]P < 0.05 *vs* the control group after treatment; n = 70.

SSIOS: Self-rating idea of suicide scale; PSQI: Pittsburgh Sleep Quality Index.

Comparison of quality of life between the two groups

After undergoing treatment for 8 wk, the observation group showed a considerably enhanced quality of life compared to that of the control group (P < 0.05; Table 4).

DISCUSSION

As a prevalent mental disorder, depression is characterized by high recurrence and disability, which greatly hampers patients' social interaction, body health, and professional ability, consequently burdening society as a whole[12]. Therefore, providing timely and suitable medical interventions for individuals with depression is of immense importance [13,14]. In this study, by observing and comparing the clinical effects of mindfulness decompression alone and mindfulness decompression combined with NET for the treatment of depression, we revealed that the overall effectiveness rate in the observation group was higher than that in the control group, suggesting that the integration of NET with simple mindfulness relaxation techniques could greatly enhance therapeutic outcomes for individuals with depression and further alleviate their clinical symptoms.

The results showed a decrease in the HAMD, SSIOS, and PSQI scores in both groups following treatment, with the observation group exhibiting better outcomes than the control group. After undergoing treatment for 8 wk, the observation group showed a noticeable improvement in their quality of life score compared to the control group. This is because mindfulness decompression therapy enables patients to better deal with negative emotions and stress, and reduces the impact of depression on sleep by cultivating patients' awareness and acceptance. Additionally, NET treatment improves the metabolic function of brain tissue, helps patients re-evaluate and adjust negative thinking patterns, and promotes sleep. The combination of these can more effectively alleviate depressive symptoms, reduce suicidal ideation, improve sleep quality and quality of life, and help patients recover.

In addition, research has discovered that inflammatory factors influence pathophysiological alterations associated with depression[15]. During the onset of depression, the levels of IL-6, IL-1β, and IL-2 increase, and the activation of immune-inflammatory pathways may affect monoamine and glutamatergic neurotransmission and contribute to the pathogenesis of severe depression in some patients[16-18]. Therefore, inflammatory factors can be used as a reflective index in patients with depression[19,20]. Research has indicated that the upregulation of IL-1β can energize and amplify the central inflammatory response, cause microglial pyroptosis, affect the plasticity of hippocampal synaptic cells, and induce and aggravate depressive symptoms[21]. IL-6 can lead to excessive hypothalamic-pituitary-adrenal activity, which in turn

Table 4 Comparison of quality of life between the two groups (mean ± SD)

Groups	Social function	Emotions	Environment	Physical health
Control group (n = 70)	16.23 ± 2.34	12.28 ± 2.16	16.56 ± 3.44	16.62 ± 3.46
Observer group (n = 70)	19.25 ± 2.76	18.54 ± 2.83	18.49 ± 2.48	19.53 ± 2.39
t value	6.983	14.710	3.808	5.790
P value	< 0.001	< 0.001	< 0.001	< 0.001

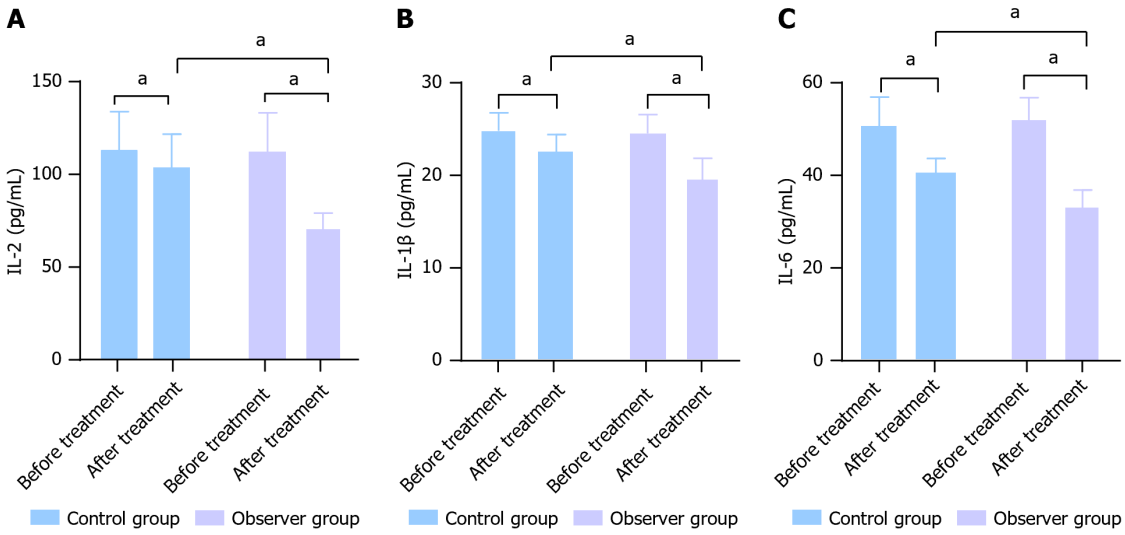

Figure 2 Changes of serum inflammatory factors in two groups of patients. $^{a}P < 0.05$.

causes fatigue, depression, and neurological symptoms[22]. The findings of this research indicated that the serum IL-1β, IL-6, and IL-2 Levels decreased following treatment in both groups. Additionally, the observation group exhibited notably improved levels of inflammatory factors compared with the control group. This indicates that mindfulness decompression combined with NET has a substantial impact on decreasing serum inflammatory factor levels in individuals with depression. This is because MBSR is a form of psychotherapy that can help patients reduce anxiety and stress and improve their mental state. Reducing psychological stress and negative emotions may reduce the production and release of inflammatory factors. In addition, NET stimulates neuronal activity by transmitting a weak current to the brain, regulates the release of neurotransmitters and the function of the neuroimmune system, and decreases the levels of pro-inflammatory substances.

This study has some limitations. We recruited a small sample of 140 individuals with depression. The selection of participants was limited, and no long-term follow-ups were conducted. In the future, the number of patients should be expanded, and a multicenter and large-sample survey should be conducted through a longitudinal study to further verify the results of this study.

CONCLUSION

Mindfulness decompression combined with NET can ameliorate depressive symptoms and improve sleep quality, effectively alleviate suicidal ideation, reduce inflammatory responses, and improve the quality of life of patients with depression. This combination exhibits remarkable clinical efficacy and deserves widespread clinical adoption.

FOOTNOTES

Author contributions: Gu ZW, Chen LP, and Huang X conceived, designed, and refined the study protocol; Gu ZW, Zhang CP, and Huang X were involved in data collection and analysis; and Gu ZW, Chen LP, and Huang X drafted the manuscript; all authors were involved in the critical review of the results and contributed to, read, and approved the final manuscript. Chen LP and Huang X contributed equally to this work as co-corresponding authors.

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ORIGINAL ARTICLE

Retrospective Study

Clinical risk factors for preterm birth and evaluating maternal psychology in the postpartum period

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Abstract

BACKGROUND

Although the specific pathogenesis of preterm birth (PTB) has not been thoroughly clarified, it is known to be related to various factors, such as pregnancy complications, maternal socioeconomic factors, lifestyle habits, reproductive history, environmental and psychological factors, prenatal care, and nutritional status. PTB has serious implications for newborns and families and is associated with high mortality and complications. Therefore, the prediction of PTB risk can facilitate early intervention and reduce its resultant adverse consequences.

AIM

To analyze the risk factors for PTB to establish a PTB risk prediction model and to assess postpartum anxiety and depression in mothers.

METHODS

A retrospective analysis of 648 consecutive parturients who delivered at Shenzhen Bao'an District Songgang People's Hospital between January 2019 and January 2022 was performed. According to the diagnostic criteria for premature infants, the parturients were divided into a PTB group (n = 60) and a full-term (FT) group (n = 588). Puerperae were assessed by the Self-rating Anxiety Scale (SAS) and Self-

rating Depression Scale (SDS), based on which the mothers with anxiety and depression symptoms were screened for further analysis. The factors affecting PTB were analyzed by univariate analysis, and the related risk factors were identified by logistic regression.

RESULTS

According to univariate analysis, the PTB group was older than the FT group, with a smaller weight change and greater proportions of women who underwent artificial insemination and had gestational diabetes mellitus (P < 0.05). In addition, greater proportions of women with reproductive tract infections and greater white blood cell (WBC) counts (P < 0.05), shorter cervical lengths in the second trimester and lower neutrophil percentages (P < 0.001) were detected in the PTB group than in the FT group. The PTB group exhibited higher postpartum SAS and SDS scores than did the FT group (P < 0.0001), with a higher number of mothers experiencing anxiety and depression (P < 0.001). Multivariate logistic regression analysis revealed that a greater maternal weight change, the presence of gestational diabetes mellitus, a shorter cervical length in the second trimester, a greater WBC count, and the presence of maternal anxiety and depression were risk factors for PTB (P < 0.01). Moreover, the risk score of the FT group was lower than that of the PTB group, and the area under the curve of the risk score for predicting PTB was greater than 0.9.

CONCLUSION

This study highlights the complex interplay between postpartum anxiety and PTB, where maternal anxiety may be a potential risk factor for PTB, with PTB potentially increasing the incidence of postpartum anxiety in mothers. In addition, a greater maternal weight change, the presence of gestational diabetes mellitus, a shorter cervical length, a greater WBC count, and postpartum anxiety and depression were identified as risk factors for PTB.

Key Words: Preterm birth; Risk factors; Postpartum psychological state; Risk model; Prediction

Core Tip: This study identified several important risk factors for preterm birth (PTB), including a greater maternal weight change, the presence of gestational diabetes mellitus, a shorter cervical length in the second trimester, a greater white blood cell count, and postpartum anxiety and depression. Based on these factors, a PTB risk prediction model was constructed by our research team, which demonstrated excellent prediction efficiency. In addition, in view of the high prevalence of negative emotions such as anxiety and depression in mothers with PTB, timely psychological intervention is necessary. These findings are helpful for promoting early intervention, reducing the adverse consequences of PTB and providing a new perspective for the management of pregnant women.

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INTRODUCTION

Preterm birth (PTB) definitions vary internationally and are generally set before 37 wk of gestation[1]. China adopts the World Health Organization's 1976 definition, considering the birth of a fetus weighing over 1000 g between 28 wk and less than 37 wk gestation as PTB[2,3]. Factors such as advancements in reproductive technologies, changes in birth policies to allow couples to have more children, and enhanced living standards have contributed to increased pregnancy complications and PTB rates, which range from 7%-15% in China, slightly higher than the rates of 6%-11% observed in developed countries[4]. PTB is the leading cause of perinatal mortality and morbidity, contributing to one-third of perinatal deaths and three-quarters of perinatal illnesses[5]. Research indicates that PTB survivors often face significant health challenges, including a high likelihood (80%) of experiencing cognitive impairments or neurological sequelae[6]. Additionally, PTB is linked to long-term complications across various bodily systems, including respiratory, digestive, and immune disorders, as well as central nervous system diseases[7]. Long-term observations further revealed that preterm infants (PTI) are at risk for sensory, motor, cognitive, and developmental issues[8], underscoring the critical need for targeted interventions and support.

The risk factors for PTB are very complex, and one of the major categories significantly related to PTB is various complications that occur during pregnancy, including intrahepatic cholestasis of pregnancy, gestational diabetes mellitus (GDM), premature rupture of membranes (PROM), placenta previa, placental abruption, fetal distress, and multiple pregnancy[9,10]. In addition to the abovementioned pregnancy complications, PTB is also related to many other factors, such as socioeconomic factors, prepregnancy physical conditions, nutritional status during pregnancy, lifestyle habits

during pregnancy, environmental and psychological factors, and reproductive history[2]. The existing frameworks for predicting PTB involve significant challenges due to the intricate web of risk factors, including genetic, environmental, and socioeconomic factors[11]. These complexities hinder accurate predictions, leading to a management approach that is often reactive rather than preventive. Consequently, there is an urgent need for the development of more sophisticated and nuanced prediction models. Such models would not only improve the accuracy of PTB predictions but also shift the paradigm from emergency care to targeted, preemptive interventions. By enhancing our predictive capabilities, we can create opportunities for developing personalized treatment plans, tailored interventions, and comprehensive support strategies, thereby significantly mitigating the health risks associated with PTB for both mothers and infants[5].

PTIs often require care in the neonatal intensive care unit, while their mothers experience the stress of physical and mental discomfort and separation from their infants[12]. This situation can increase the risk of postpartum anxiety and depression for mothers, who worry about their PTIs' health, survival, and future development[13]. This study aimed to analyze the clinical risk factors for PTB and assess postpartum anxiety and depression in mothers, providing a theoretical basis for PTB treatment and prevention. Future research should explore innovative interventions to support both PTIs and their mothers, enhancing care strategies and psychological support to mitigate the impact of PTB on families.

MATERIALS AND METHODS

Sample source

In this retrospective study, 1041 parturients who delivered at Shenzhen Bao'an District Songgang People's Hospital between January 2019 and January 2022 were selected as study participants, and their clinical data were collected for regression analysis.

Criteria for patient enrollment and exclusion

The inclusion criteria for patients were as follows: All patients who underwent standardized and regular prenatal examinations at our hospital during pregnancy and delivered at our hospital and had complete clinical data.

The exclusion criteria were as follows: Patients with medical PTB, such as PTB due to placenta accreta, threatened uterine rupture, chorioamnionitis, and pregnancy-induced hypertension; patients with early termination of pregnancy due to placental abruption, fetal distress, fetal growth and development delay, *etc.*; patients who were not advised to continue pregnancy due to clinical safety considerations; patients who underwent cervical cerclage during or before pregnancy due to "cervical insufficiency"; and patients with a prior history of conization of the cervix.

Sample screening

In this study, a total of 648 eligible parturients were screened according to the inclusion and exclusion criteria. According to the diagnostic criteria for PTIs (28 wk ≤ gestational age < 37 wk and fetal weight ≥ 1000 g), the parturients were divided into a PTB group (n = 60) and a full-term (FT) group (n = 588).

Clinical data collection

Clinical data and laboratory-related indicators were collected from electronic medical records and outpatient records. The clinical data collected included age, prepregnancy body mass index (BMI), prepregnancy disease history (history of malignant tumors, hyperthyroidism, hypothyroidism, diabetes, and heart disease), weight change during pregnancy, ethnicity, parity, mode of conception (spontaneous conception or conception by assisted reproductive technology), history of tobacco and alcohol exposure during pregnancy, whether nutritional supplements were used during pregnancy, and whether regular physical activity was performed during pregnancy (30 min of low-intensity exercise daily). Laboratory indicators included the last routine blood and leucorrhea examination before delivery, the last ultrasound examination before delivery, and the cervical length measured by transvaginal ultrasound in the second trimester. The women were assessed for negative emotions in the postpartum period using the Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS)[14]. Both scales consist of 20 items answered using a 4-point scale. The standard score was the integer obtained by multiplying the total score of the 20 items by 1.25. Mothers with a standard SAS score ≥ 50 points were considered to have anxiety, and those with a standard SDS score ≥ 53 points were considered to have depression.

Outcome measures

The primary outcome measures were as follows: Univariate analysis was performed to identify factors influencing PTB, and the risk factors for PTB were further determined using logistic regression.

The secondary outcome measures were as follows: The postpartum SAS and SDS scores were recorded to screen for anxiety and depression symptoms.

Statistical methods

In this study, R language 4.1.1 software (R Foundation for Statistical Computing, Vienna, Australia) was used for data sorting and analysis, and a prediction model was established. Logistic regression was used to screen the influencing factors, and their clinical value was verified by receiver operating characteristic (ROC) curve analysis. Data analysis and visualization were performed with Graph Pad Prism 8.0. Normally distributed data are statistically described as the mean ± SD; comparisons between two groups were performed with a t test, whereas intergroup comparisons were performed

with an independent sample t test, and intragroup comparisons were performed with a paired *t* test. The χ^2 test was used to compare count data. In all tests, a significance level of 5% ($P < 0.05$) was adopted.

RESULTS

Clinical data analysis

The clinical data of the two groups were compared. The results showed that the PTB group was older than the FT group, with a smaller pregnancy weight change and greater proportions of women who underwent artificial insemination and had GDM (all $P < 0.05$, Table 1); no significant differences were identified in other clinical data ($P > 0.05$, Table 1).

Laboratory index analysis

Compared with the FT group, the PTB group had a significantly greater proportion of women with reproductive tract infections, greater white blood cell (WBC) counts, shorter cervical lengths in the second trimester, and lower neutrophil counts ($P < 0.001$, Table 2).

Assessment of adverse emotions

We compared postpartum anxiety and depression scores between the two groups. The results revealed lower postpartum SAS and SDS scores in the FT group than in the PTB group ($P < 0.0001$, Figure 1). Moreover, more mothers in the PTB group than in the FT group experienced symptoms of anxiety and depression, as indicated by the chi-square test ($P < 0.001$, Table 3).

Analysis of risk factors for PTB

We assigned values to the abovementioned factors with statistical significance (Table 4) and then used the backward LR method to identify risk factors for PTB. A greater maternal weight change, the presence of GDM, a shorter cervical length in the second trimester, a greater WBC count, and the presence of maternal anxiety and depression were confirmed to be risk factors for PTB (Table 5, $P < 0.01$).

Prediction model construction

A risk prediction model based on logistic regression coefficients was built. Since anxiety and depression are postpartum factors, we excluded them as predictors of PTB. We then constructed a risk formula with a risk score calculated as follows: -1.453 × maternal weight change + 1.577 × GDM + -3.784 × cervical length in the second trimester + 2.255 × WBC count. Then, we compared the risk scores between the FT and PTB groups, and a significantly lower risk score was found in the FT group than in the PTB group ($P < 0.0001$, Figure 2A). In addition, the area under the ROC curve (AUC) of the risk score for predicting PTB in pregnant women was 0.937, with a specificity of 90.00% and a sensitivity of 86.73% (Figure 2B).

DISCUSSION

Though it remains to be further elucidated, the pathogenesis of PTB, according to the available findings, is associated with multiple factors, such as pregnancy complications, maternal socioeconomic factors, living habits (smoking, drinking, and eating habits, *etc.*), reproductive history (history of abortion, history of premature birth, the use of assisted reproductive technology, *etc.*), environmental and psychological factors, antenatal care, and nutritional status[15]. PTB is known to be extremely harmful to preterm infants' families and leads to a high mortality rate of PTIs, and those who survive may experience a variety of sequelae and complications[16], imposing a substantial burden on the families of PTIs and society. In this context, it would be beneficial to be able to predict PTB in advance, which would provide more opportunities for early intervention to reduce the negative emotions caused by PTB and the consequences of PTB.

In this study, we analyzed the clinical risk factors for PTB. According to related research[17], PTB and its associated complications are the major factors leading to neonatal death, with approximately 15% of premature babies dying in the neonatal stage. According to World Health Organization statistics[18], there are more than 13 million PTIs worldwide, with a PTB rate of nearly 10%, while the rate in Asia is approximately 9%. The PTB rate in this study was 9.3%, which is consistent with the existing records. In our study, a greater maternal weight change, the presence of GDM, a shorter cervical length in the second trimester, a greater WBC count, and the presence of maternal anxiety and depression were risk factors for PTB.

Overweight and obesity increase the risk for high birth weight and PTB in offspring[19]. On the other hand, an underweight BMI prior to conception is associated with a reduced risk of PTB. In all initial weight categories, insufficient weight change in pregnant women is linked to an increased incidence of spontaneous PTB and PROM-related PTB (PROM-PTB)[20]. Generally, an increase in weight in pregnant women predicts an increase in the probability of all types of PTB[21]. Therefore, maintaining normal weight gain is one of the keys to reducing PTB. GDM, a type of diabetes that pregnant women may experience, occurs during pregnancy and usually disappears after delivery[22]. This may lead to high blood sugar levels in pregnant women, exerting some negative effects on the mother and fetus. Research has shown that GDM may cause a fetus to be too large because too much glucose may be absorbed and converted into fat[23]. An oversized fetus can induce PTB because early labor may be triggered, or doctors may choose early delivery because the

Table 1 Comparison of clinical data

Categories		Preterm birth group (*n* = 60)	Full term group (*n* = 588)	*P* value
Age				0.003[b]
	≥ 35 years old	47	341	
	< 35 years old	13	247	
Prenatal BMI				0.355
	≥ 23 kg/m^2	42	376	
	< 23 kg/m^2	18	212	
History of pre-pregnancy diseases				0.540
	With	5	35	
	Without	55	553	
Maternal weight change (kg)		8.8 ± 4.7	12.1 ± 3.9	< 0.001[c]
Parity				0.608
	Primipara	47	441	
	Multipara	13	147	
Mode of conception				0.005
	Spontaneous conception	52	559	
	Artificial insemination	8	29	
History of alcohol and tobacco exposure during pregnancy				0.361
	With	5	35	
	Without	55	553	
Nutritional supplements during pregnancy				
	Folic acid supplementation in early pregnancy	47	417	0.252
	Multivitamin supplements in the second trimester	49	441	0.303
	No nutritional supplements during pregnancy	4	41	0.771
Regular physical activity				0.562
	Yes	9	106	
	No	51	482	
Gestational diabetes mellitus				0.001[b]
	Yes	11	35	
	No	49	553	

[b]*P* < 0.01.
[c]*P* < 0.001.
BMI: Body mass index.

fetus is too large. In addition, GDM may increase the risk of pregnancy-induced hypertension and preeclampsia, further increasing the risk of PROM and leading to PTB. Furthermore, GDM can cause maternal blood sugar levels to be difficult to control, which can affect fetal development and increase the risk of PTB. Previously, Pigatti Silva *et al*[21] reported that pregnancy complications were risk factors for PTB. However, in their research, pregnancy complications included pregnancy-induced hypertension, GDM, intrahepatic cholestasis of pregnancy, prenatal and postpartum hemorrhage, placental abnormalities, *etc.*, which cannot demonstrate the role of GDM as an independent risk factor for PTB. In contrast, Dekker *et al*[24] reported that GDM was an independent risk factor for PTB, suggesting that maternal blood glucose changes should be monitored in a timely manner and that early detection and treatment should be carried out to improve pregnancy outcomes.

Table 2 Comparison of laboratory indexes of patients

Categories	Preterm birth group (*n* = 60)	Full term group (*n* = 588)	*P* value
Reproductive tract infection	13	65	0.023[a]
Cervical length in the second trimester (mm)	24.7 ± 3.3	32.9 ± 4.8	< 0.001[c]
White blood cell count (× 10^9/L)	11.6 ± 2.4	9.5 ± 2.4	< 0.001[c]
Neutrophil percentage	0.74 ± 0.05	0.86 ± 0.07	< 0.001[c]

[a]*P* < 0.05.
[c]*P* < 0.001.

Table 3 Comparison of anxiety and depression symptoms

Group	Number of parturients with anxiety	Number of parturients with depression	Number of parturients with anxiety and depression
Preterm birth group (*n* = 60)	43	45	43
Full term group (*n* = 588)	191	251	191
χ^2	36.232	22.910	36.232
P value	< 0.001[c]	< 0.001[c]	< 0.001[c]

[c]*P* < 0.001.

Table 4 Assignment table

Factors	Assignment
Age	≥ 35 years old = 1, < 35 years old = 0
Maternal weight change (kg)	≥ 10.45 = 1, < 10.45 = 0
Mode of conception	Artificial insemination = 1, spontaneous conception = 0
Gestational diabetes mellitus	With = 1, without = 0
Reproductive tract infection	With = 1, without = 0
Cervical length in the second trimester (mm)	≥ 29.05 = 1, < 29.05 = 0
White blood cell count (× 10^9/L)	≥ 9.35 = 1, < 9.35 = 0
Neutrophil percentage	≥ 0.85 = 1, < 0.85 = 0
Maternal anxiety and depression	With = 1, without = 0
Delivery status	Premature = 1, full-term = 0

In normal adult nonpregnant women, the cervix is usually 25 mm-30 mm in length. Ultrasonic measurement of cervical length requires a rigorous sagittal section to show the morphology of the internal and external cervical os and the length of the cervical canal[25]. Under normal circumstances, the internal cervical os is closed and has a certain tension that prevents the fetus and its appendages (such as the fetal membrane and placenta) from moving toward the cervical canal. The cervix gradually matures as gestational age increases. However, premature maturation of the cervix can cause the cervix to shorten significantly, causing the cervix to be squeezed as the fetus moves down[26]. This further shortens the length of the cervical canal and even leads to the expansion of the external cervix and the discharge of the mucus plug, ultimately leading to an increased risk of PTB. Inflammation is the physiological response of the body to infection, tissue injury or other stimuli and can lead to the release of inflammatory mediators and cytokines[27]. The WBC count is an index that directly reflects the inflammatory reaction in patients. Infection is one of the most common causes of inflammation-related PTB, and bacterial, viral or other microbial infections can increase the amount of WBCs in the body[28]. The release of massive amounts of inflammatory mediators following an inflammatory response may lead to uterine contraction and cervical relaxation, resulting in premature labor. Postpartum anxiety and PTB affect and interact with each other[29]. Postpartum anxiety may increase the risk of PTB, and PTB itself may also increase the incidence of

Table 5 Analysis of risk factors for preterm birth

Factors	β	Standard error	χ^2	*P* value	OR	95%CI	
						Lower bound	Upper bound
Age	0.650	0.428	2.315	0.128	1.916	0.829	4.429
Maternal weight change	-1.453	0.396	13.456	< 0.001[c]	0.234	0.108	0.508
Mode of conception	0.967	0.674	2.057	0.151	2.630	0.702	9.855
Gestational diabetes mellitus	1.577	0.586	7.244	0.007[b]	4.839	1.535	15.254
Reproductive tract infection	0.811	0.500	2.629	0.105	2.250	0.844	5.997
Cervical length in the second trimester	-3.784	0.521	52.804	< 0.001[c]	0.023	0.008	0.063
White blood cell count	2.255	0.512	19.420	< 0.001[c]	9.537	3.498	26.004
Maternal anxiety and depression	1.802	0.391	21.301	< 0.001[c]	6.064	2.821	13.036

[b]*P* < 0.01.
[c]*P* < 0.001.
OR: Odds ratio; CI: Confidence interval.

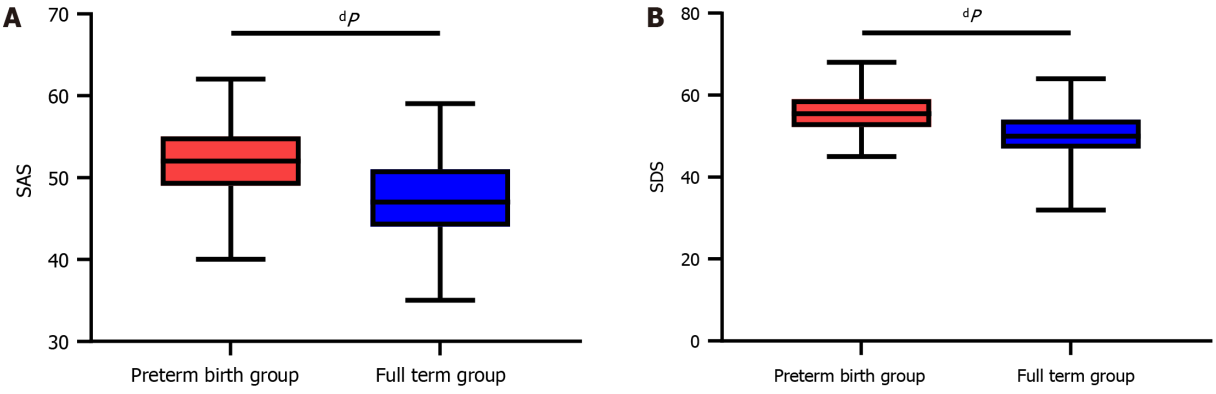

Figure 1 Comparison of postpartum maternal Self-rating Anxiety Scale and Self-rating Depression Scale scores. A: Comparison of postpartum Self-rating Anxiety Scale scores between two groups; B: Comparison of postpartum Self-rating Depression Scale scores between two groups. SAS: Self-rating Anxiety Scale; SDS: Self-rating Depression Scale. [d]*P* < 0.0001.

postpartum anxiety[30]. Preterm mothers face multiple forms of distress and anxiety, including separation anxiety and concerns about the health and development of their baby[31]. Therefore, early psychological support and intervention are crucial for preterm mothers. Emotional support, education and counseling can help mothers cope with anxiety and enhance their coping skills and emotional regulation, thereby reducing the occurrence and impact of postpartum anxiety and positively impacting the health and development of PTIs. Therefore, attention should be given to mental health in the care of preterm mothers, and comprehensive support and care should be provided to promote the overall well-being of PTIs and their mothers. At the end of the study, we built a risk model based on the identified risk factors. It was found that the AUC of the risk prediction model was greater than 0.9, demonstrating that this model is an excellent potential predictive tool.

However, there are still some limitations in this study. First, the participants were all from our hospital, which is a single center, leading to a small sample size. Second, although the model was established, the influencing factors were not systematically reviewed from an evidence-based perspective, and the included indicators were not comprehensive. Furthermore, there may be statistical biases in the data collection and analysis process. Therefore, whether the prediction model can be widely used in clinical practice still needs further verification and discussion.

CONCLUSION

This study highlights the complex interaction between postpartum anxiety and PTB, *i.e.*, that maternal anxiety may be a potential risk factor for PTB, and PTB may increase the incidence of postpartum anxiety in mothers. In addition, the study identified a greater maternal weight change, the presence of GDM, a shorter cervical length, a greater WBC count, and the presence of postpartum anxiety and depression as risk factors for PTB.

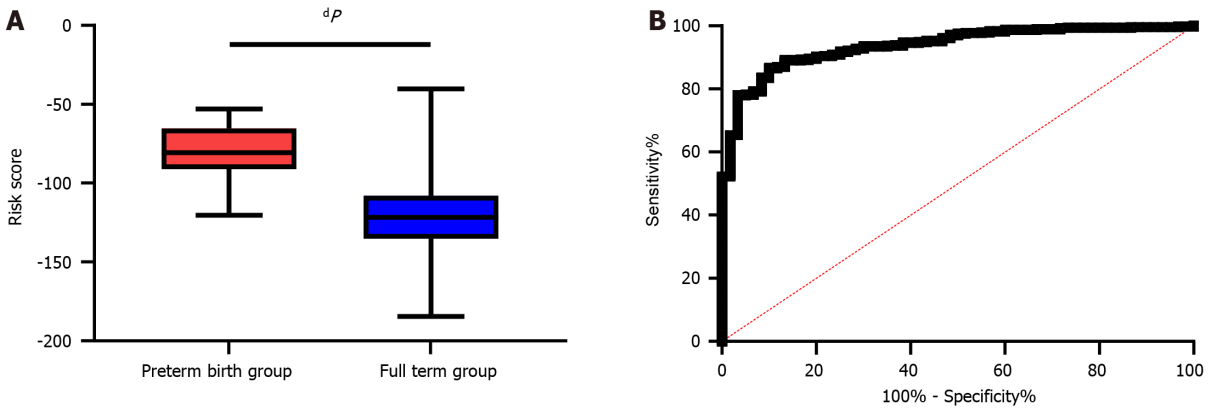

Figure 2 Logistic regression model of the risk score in predicting preterm birth and the receiver operating characteristic curve. A: Risk scores of preterm birth group and full term group; B: Receiver operating characteristic curve of the risk score in predicting preterm birth. $^{d}P < 0.0001$.

FOOTNOTES

Author contributions: Chen JJ designed the research, wrote the first manuscript, conducted the analysis and provided guidance for the research; Chen JJ, Chen XJ, She QM, Li JX and Luo QH contributed to conceiving the research and analyzing data. All authors reviewed and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Effects of intensive psychological intervention on treatment compliance, psychological status, and quality of life of patients with epilepsy

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Abstract

BACKGROUND

Epilepsy is a nervous system disease characterized by recurrent attacks, a long disease course, and an unfavorable prognosis. It is associated with an enduring therapeutic process, and finding a cure has been difficult. Patients with epilepsy are predisposed to adverse moods, such as resistance, anxiety, nervousness, and anxiety, which compromise treatment compliance and overall efficacy.

AIM

To explored the influence of intensive psychological intervention on treatment compliance, psychological status, and quality of life (QOL) of patients with epilepsy.

METHODS

The clinical data of 105 patients with epilepsy admitted between December 2019 and July 2023 were retrospectively analyzed, including those of 50 patients who underwent routine intervention (control group) and 55 who underwent intensive psychological intervention (research group). Treatment compliance, psychological status based on the Self-Rating Anxiety Scale (SAS) and Depression Scale Self-Rating Depression Scale (SDS) scores, hope level assessed using the Herth Hope Scale (HHS), psychological resilience evaluated using the Psychological Resilience Scale, and QOL determined using the QOL in Epilepsy-31 Inventory (QOLIE-31) were comparatively analyzed.

RESULTS

Treatment compliance in the research group was 85.5%, which is significantly

better than the 68.0% of the control group. No notable intergroup differences in preinterventional SAS and SDS scores were identified ($P > 0.05$); however, after the intervention, the SAS and SDS scores decreased significantly in the two groups, especially in the research group ($P < 0.05$). The two groups also exhibited no significant differences in preinterventional HHS, Connor-Davidson Resilience Scale (CD-RISC), and QOLIE-31 scores ($P > 0.05$). After 6 months of intervention, the research group showed evidently higher HHS, CD-RISC, tenacity, optimism, strength, and QOLIE-31 scores ($P < 0.05$).

CONCLUSION
Intensive psychological intervention enhances treatment compliance, psychological status, and QOL of patients with epilepsy.

Key Words: Intensive psychological intervention; Epilepsy; Treatment compliance; Psychological status; Quality of life

Core Tip: Epilepsy is a common chronic disease of the nervous system. Current treatment of epilepsy is mainly based on symptomatic treatment. Patients with poorly controlled seizures are at a higher risk of depression than those with well-controlled seizures. This study mainly explores the influence of intensive psychological intervention on the treatment compliance, psychological status, and quality of life of patients with epilepsy.

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INTRODUCTION

Epilepsy is a common chronic disease of the nervous system that is characterized by a persistent predisposition for seizures, which is not caused by any direct central nervous system injury, but by the neurobiological, cognitive, psychological, and social consequences of epileptic seizures[1-3]. The prevalence of epilepsy is approximately 0.5%-1%[4], with a slightly higher incidence in men than in women, especially in the youngest and oldest age groups[5,6]. Genetic susceptibility to seizures varies, as does the distribution of some environmental risk factors, which may explain the global heterogeneity of the incidence, course, and consequences of epilepsy[7]. In addition to the recurrence of seizures, the underlying etiology and adverse effects of treatment significantly affect the patient's quality of life (QOL) and make the disease a complex health burden[8].

The treatment of epilepsy is currently based on symptomatic treatment[9]. Most patients can achieve seizure freedom through the first two appropriate drug trials. Those who fail to achieve a satisfactory response are defined as resistant and can eventually develop refractory epilepsy[10,11]. Psychiatric disorders are relatively rare but serious complications of epilepsy[12]. Current epidemiological research has shown a 5.6% incidence of psychiatric disorders in an unselected sample of patients with epilepsy[13]. In addition, patients with poorly controlled seizures are at a higher risk of depression than those with well-controlled seizures[14]. However, anxiety is not currently of sufficient interest in patients with epilepsy, even though it is more prevalent than depression[15]. Because of the long course of epilepsy and the unpredictability of seizures, patients are prone to nervous, anxious, and other negative emotions, leading to decreased treatment compliance, which is not conducive to the outcome of the disease. In the lengthy process of antiepileptic treatment, recurrent episodes and the huge psychological pressure caused by economic burden and social discrimination will seriously affect the normal work and life of patients[16]. Furthermore, the level of self-identification of patients with epilepsy also diminishes, leading to behavioral abnormalities, such as inner pain[17]. Therefore, psychological intervention for patients with epilepsy is a crucial feature of clinical treatment. This study retrospectively analyzed the clinical data of patients with epilepsy to explore the impact of intensive psychological intervention on treatment compliance, psychological status, and QOL of these patients.

MATERIALS AND METHODS

Study participants

This retrospective analysis included 105 patients with epilepsy admitted between December 2019 and July 2023. The inclusion criteria were the following: (1) Meeting the epilepsy diagnosis criteria of the International League Against Epilepsy in 2017; (2) aged 18-60 years; (3) course of epilepsy ≥ 6 months; (4) use of antiepileptic drugs ≥ 3 months; (5) no communication or hearing impairment; (6) normal comprehension and communication skills and certain reading compre-

hension ability; and (7) complete clinical and follow-up data. The exclusion criteria were as follows: (1) Psychogenic pseudoepileptic seizures; (2) history of epilepsy-related surgery; (3) severe mental and neurological complications; (4) diagnosis of malignant tumor(s); (5) refusal to undergo neuropsychological evaluation; and (6) incomplete clinical data.

Research methods

Patients were divided into either the control or research group based on different intervention methods documented in their records, with 50 cases in the control group and 55 cases in the research group. Patients in the control group underwent routine intervention based on the clinical treatment of the disease, *i.e.*, safe nursing for the onset of the disease and adverse reactions, and oral explanation of disease-related knowledge. The main measures were as follows: (1) A protective belt, mouth opener, and other items were used to prevent bed falling and tongue biting, and local pressure was avoided as much as possible; and (2) valproic acid was administered to patients with generalized seizures, and antiviral therapy was strengthened for those with viral encephalitis. During seizures, phenobarbital sodium was injected intramuscularly or diazepam intravenously.

In addition to the above measures, those in the research group underwent intensive psychological intervention: (1) The patients and their families were assisted in establishing a correct understanding of the disease and reducing their psychological burden by providing health education manuals, watching videos, listening to audio presentations, holding seminars, *etc*.; (2) the patients were encouraged to participate in social activities more actively to help them realize their social values and improve their self-esteem; (3) doctor-patient communication was enhanced, and effective communication channels were established; medical staff patiently listened to patients' complaints and avoided indifference and impatience so that patients felt cared for and supported; (4) the medical staff promoted communication between the patients and their families, encouraged the patients' families to actively participate in nursing, and took good care of the patients in life; (5) the patients' psychological state was monitored, and any psychological abnormalities were reported promptly to coordinate with the medical staff in conducting psychological counseling to manage patients' negative emotions and enhance their confidence; (6) patient-patient communication was also encouraged to exchange self-management experience, support each other, share rehabilitation experience, and establish a relaxed and comfortable ward environment; and (7) a long-term and effective consultation platform was established, through which patients and their families can consult on treatment-related issues in or out of the hospital, while allowing doctors to regularly follow-up discharged patients' illness and recent conditions. All patients underwent a 6-month follow-up.

Outcome measures

Determination of treatment compliance. Complete compliance: The patient can completely follow the doctor's advice to accomplish various interventions and take the medication on time at the dosage prescribed during the treatment process. Partial compliance: The patient can partially accomplish various interventions and follow the instructions on medication time and dosage according to the doctor's advice. Noncompliance: The patient can occasionally follow the doctor's advice for treatment or cooperate with treatment when the condition worsens but does not understand the side effects of drugs. Compliance = complete compliance + partial compliance.

Psychological state assessment. Patients' negative emotions before and 6 months after intervention were evaluated using Zung's Self-Rating Anxiety Scale (SAS) and Scale Self-Rating Depression Scale (SDS), with the score in positive association with the severity of anxiety and depression.

Hope level evaluation. The hope level of patients before and 6 months after intervention was assessed using the Herth Hope Scale (HHS). The scale contains three dimensions, namely, temporality and future orientation (T), positive readiness and expectancy (P), and interconnectedness (I). Each dimension has four items that can be classified into four grades, with the possible total score ranging from 12 to 48. A higher score corresponds to a higher hope level, with 12-23, 23-35, and 35-48 points indicating low, medium, and high levels of hope, respectively.

Psychological resilience evaluation: We used the Connor-Davidson Resilience Scale (CD-RISC) to assess patients' psychological resilience before and 6 months after intervention. The scale consists of 25 items that fall into three dimensions: tenacity, strength, and optimism. The scale uses a five-point scoring method, with 0, 1, 2, 3, and 4 corresponding to never, rarely, sometimes, often, and always, respectively. The total score (range: 0-100) = tenacity score + strength score + optimism score. A higher score indicates better psychological resilience.

QOL of patients with epilepsy. QOL was assessed before and 6 months after the intervention using the QOL in Epilepsy-31 Inventory (QOLIE-31). QOLIE-31 exhibited good reliability and validity in Chinese adult patients with epilepsy. The scale consists of seven components: Seizure worry, overall QOL, emotional well-being, energy/fatigue, cognitive functioning, medication effects, and social functioning, each scored on a percentage scale. Scoring system: The score of each item is converted to its corresponding points (0-100), and the total score of each dimension is obtained by dividing the sum of the conversion points of the items in each dimension by the total number of items. The higher the score, the better the QOL. Finally, the total score of the seven dimensions is multiplied by the weight and then added to obtain the total QOL score.

Statistical analysis

Data analyses were performed using SPSS version 25.0, and statistical significance was set at P-value < 0.05. Measurement data are expressed as mean ± SD. Student's t-test was used for intergroup comparisons of means and paired t-tests for intragroup comparisons before and after intervention. The rank-sum test was used to compare the ranked data. Count data are expressed as percentages, for which the chi-square test was used for comparison.

RESULTS

General information

Comparison of general data revealed no statistical intergroup differences in age, sex, course of disease, monthly frequency of attacks, and number of epileptic seizure types ($P > 0.05$), indicating that the two groups of patients were comparable (Table 1).

Patient compliance

The research group (85.5%) exhibited significantly higher treatment compliance than the control group (68.0%) (Table 2).

Psychological states of the two patient groups

The two groups showed similar SAS and SDS scores before intervention ($P > 0.05$); a marked reduction was observed in SAS and SDS scores in both groups after intervention, with even lower scores in the research group ($P < 0.05$; Figure 1).

Hope level of patients in both groups

The preinterventional T, P, and I scores and overall hope level were similar between the research and control groups ($P > 0.05$). After the intervention, the T, P, and I scores of both groups and the overall hope level increased statistically, especially in the research group ($P < 0.05$; Table 3).

Patient psychological resilience

The two groups did not differ significantly in the preinterventional total and individual dimension scores for CD-RISC ($P > 0.05$). Both groups showed significant increases in the total score and scores for tenacity, optimism, and strength at 6 months after intervention, with even higher scores in the research group ($P < 0.05$; Table 4).

QOLIE-31 scores

No notable intergroup differences were observed in the preinterventional total and individual dimension scores for QOLIE-31 ($P > 0.05$). After 6 months of intervention, the total and individual dimension scores for QOLIE-31 in both groups increase significantly, with higher scores in the research group than in the control group ($P < 0.05$; Table 5).

DISCUSSION

Epilepsy is a chronic nervous system disease strongly associated with genetic factors, surgery, febrile convulsions, and brain trauma[18]. Given the current lack of specific therapeutic agents, the disease is treated based on the principles of improving patient QOL and controlling disease onset. Patients with epilepsy are often affected by intermittent seizure episodes, which restrict their life and work and severely affect their psychological state, resulting in a severely reduced QOL. Therefore, psychological intervention has important implications for the prognosis of patients with epilepsy.

This study mainly investigated the influence of intensive psychological intervention on the compliance, psychological state, and QOL of patients with epilepsy. The results showed a significant decrease in SAS and SDS scores and an increase in HHS, CD-RISC, tenacity, optimism, strength, and QOLIE-31 scores in patients with epilepsy who underwent intensive psychological intervention. Therefore, intensive psychological intervention promotes the improvement of the mental state and QOL of patients with epilepsy. Recurrent seizures may affect the function of the limbic system without directly influencing the development of depression and increase patients' susceptibility to mental disorders and social stress[19]. A bidirectional relationship has also been established between epilepsy and depression[20]. In routine nursing, patients' psychological problems can easily be overlooked. In contrast, intensive psychological intervention is a more detailed and optimized intervention mode that further strengthens the patient's psychological state[21]. It extends and expands the advantages of the original intervention model, extends the research on the relevant factors affecting the mental state, and implements the corresponding measures. Strengthening health education during intensive psychological nursing can help patients correctly understand the disease and reduce their psychological burden. Furthermore, intensive psychological intervention monitors the patient's psychological adjustment and enables the development of intervention strategies that can fully meet the needs of patients, minimize external causes of psychological stress, and enhance their psychological coping ability. Cognition, as the intermediary of emotional and behavioral responses, has a fundamental influence on the occurrence and changes in emotions and behaviors[22]. Intensive psychological intervention helps patients establish correct awareness about epilepsy through scientific and rational dialogues, relieves psychological conflicts, guides patients in expressing their depression, and helps regulate their emotions, thereby improving their views and attitudes and mitigating their irrational beliefs.

Furthermore, this study found that the treatment compliance of patients with epilepsy under intensive psychological intervention was 85.5%, which was significantly better than the 68.0% compliance rate of the routine intervention group. Depression and anxiety influence treatment compliance[23]. Depression and anxiety can affect patients' adherence to treatment for several reasons. First, the expectation of treatment response is an essential component of patients' treatment compliance, whereas recurrent seizures can affect patients' motivation and confidence in treatment efficacy. Anxiety itself has various presentations, such as panic attacks, generalized anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder[24], among which generalized anxiety disorder has the greatest influence on treatment compliance[25]. Moreover, the postinterventional T, P, I, and QOL scores in the research group were higher than those in

Table 1 Comparison of general information, *n* (%)

	Control group (*n* = 50)	Research group (*n* = 55)	χ^2/t	*P* value
Gender				
Male	24 (48.0)	29 (52.7)	0.234	0.629
Female	26 (52.0)	26 (47.3)	0.725	0.470
Age (yr)	36.65 ± 6.48	37.29 ± 6.97		
Disease course (months)	18.24 ± 4.38	18.39 ± 4.33	0.451	0.653
Monthly frequency of seizure attacks (times)	6.15 ± 3.85	6.27 ± 3.91	0.469	0.640
Seizure type			0.856	0.652
Simple focal seizures	5 (10.0)	3 (5.5)		
Absence seizures	16 (32.0)	20 (36.3)		
Grand mal seizures	29 (58.0)	32 (58.2)		

Table 2 Comparison of patient compliance, *n* (%)

	Control group (*n* = 50)	Research group (*n* = 55)	χ^2	*P* value
Complete compliance	20 (40.0)	31 (56.4)	4.525	0.033
Partial compliance	14 (28.0)	16 (29.1)		
Non-compliance	16 (32.0)	8 (14.5)		
Compliance	34 (68.0)	47 (85.5)		

Table 3 Comparison of hope level

		Control group (*n* = 50)	Research group (*n* = 55)	*t*	*P* value
Temporarily and future orientation (T)	Before intervention	7.86 ± 0.93	7.82 ± 1.12	0.198	0.843
	6 months after intervention	9.90 ± 1.39[a]	11.07 ± 1.51[a]	4.118	< 0.0001
Positive readiness and expectancy (P)	Before intervention	8.26 ± 1.31	8.49 ± 1.17	0.950	0.344
	6 months after intervention	10.50 ± 1.82[a]	12.80 ± 1.43[a]	7.234	< 0.0001
Interconnectedness (I)	Before intervention	8.56 ± 1.75	9.13 ± 1.52	1.786	0.077
	6 months after intervention	11.54 ± 2.16[a]	13.58 ± 1.80[a]	5.274	< 0.0001
Overall hope level	Before intervention	24.68 ± 2.30	25.44 ± 2.42	1.646	0.103
	6 months after intervention	31.94 ± 2.80[a]	37.48 ± 3.25[a]	9.313	< 0.0001

[a]*P* < 0.05 *vs* before intervention in the same group.

the control group, indicating high acceptance of the intensive psychological intervention model among patients with epilepsy, which, consequently, improved their hope level, changed their coping styles, and increased their QOL. People with epilepsy generally have a lower QOL, especially in terms of seizure worry and medication effects. Patients generally have a strong fear of disease recurrence, which may be related to the pain caused by the seizure itself or to the fear of shame related to others witnessing such episodes, resulting in reduced compliance with medication. Intensive psychological intervention can strengthen patients' memories of successful cases, happiness, and warmth; increase their feelings of support from society and their families and reduce their seizure worry. In addition, "happy factor" feedback intervention can enhance patients' sense of social identity and participation and promote in them a positive attitude in receiving disease treatment, which can obviously improve their QOL.

Because of its design, this study has some limitations. The retrospective design did not allow for the randomization of the two groups of patients, which would have compromised the similarity of patients within the groups. In addition, retrospective secondary data analysis carries the risk of information bias, especially with incomplete records encountered in such studies. The sample size may also be too small to reveal differences between the two groups. Therefore, the similarity of clinical outcomes between the two groups in our investigation may be a type II error. Furthermore, the study

Table 4 Comparison of psychological resilience level

		Control group (*n* = 50)	Research group (*n* = 55)	*t*	*P* value
Tenacity	Before intervention	24.14 ± 4.07	24.53 ± 3.71	0.514	0.609
	6 months after intervention	33.10 ± 5.41[a]	36.13 ± 5.26[a]	2.908	0.044
Optimism	Before intervention	9.46 ± 2.58	9.75 ± 2.41	0.595	0.553
	6 months after intervention	19.02 ± 3.31[a]	22.15 ± 2.79[a]	5.255	< 0.0001
Strength	Before intervention	7.94 ± 2.41	8.60 ± 2.09	1.503	0.136
	6 months after intervention	11.00 ± 1.58[a]	13.60 ± 1.31[a]	9.210	< 0.0001
Total score	Before intervention	41.54 ± 5.93	42.87 ± 4.33	1.321	0.189
	6 months after intervention	63.12 ± 6.60[a]	71.87 ± 6.11[a]	7.054	< 0.0001

[a]*P* < 0.05 *vs* before intervention in the same group.

Table 5 Comparison of quality of life in Epilepsy-31 Inventory score

		Control group (*n* = 50)	Research group (*n* = 55)	*t*	*P* value
Seizure worry	Before intervention	42.78 ± 6.21	43.15 ± 8.12	0.260	0.795
	6 months after intervention	53.10 ± 9.34[a]	61.82 ± 7.20[a]	5.385	< 0.0001
Overall quality of life	Before intervention	44.24 ± 6.32	45.78 ± 4.70	1.425	0.157
	6 months after intervention	55.66 ± 8.30[a]	63.45 ± 7.19[a]	5.152	< 0.0001
Emotional well-being	Before intervention	48.58 ± 5.41	47.64 ± 6.20	0.825	0.411
	6 months after intervention	58.34 ± 9.94[a]	69.20 ± 8.62[a]	5.995	< 0.0001
Energy/fatigue	Before intervention	50.46 ± 6.28	48.16 ± 7.86	1.646	0.103
	6 months after intervention	58.04 ± 7.13[a]	69.71 ± 8.36[a]	7.658	< 0.0001
Cognitive functioning	Before intervention	49.80 ± 3.94	51.02 ± 5.04	1.372	0.173
	6 months after intervention	59.72 ± 6.55[a]	70.69 ± 6.56[a]	7.021	< 0.0001
Medication effects	Before intervention	40.14 ± 7.72	42.22 ± 6.49	1.499	0.137
	6 months after intervention	57.50 ± 6.84[a]	66.18 ± 5.71[a]	7.081	< 0.0001
Social functioning	Before intervention	54.12 ± 6.38	53.82 ± 6.20	0.244	0.808
	6 months after intervention	63.88 ± 5.63[a]	71.05 ± 6.56[a]	5.981	< 0.0001
Total score	Before intervention	48.97 ± 2.33	49.13 ± 6.04	0.176	0.861
	6 months after intervention	59.13 ± 3.54[a]	68.32 ± 3.34[a]	14.578	< 0.0001

[a]*P* < 0.05 *vs* before intervention in the same group.

period was too short. A well-designed, randomized, controlled trial with prospective data collection and sample size calculations is needed to confirm our findings and evaluate the relationship between long-term clinical outcomes.

CONCLUSION

In conclusion, intensive psychological intervention for patients with epilepsy can help manage positive and negative effects, enhance treatment compliance, enable patients to actively cope with disease-related problems, and increase QOL. However, given the shortcomings of this study, further studies involving more cases and a longer research period are needed.

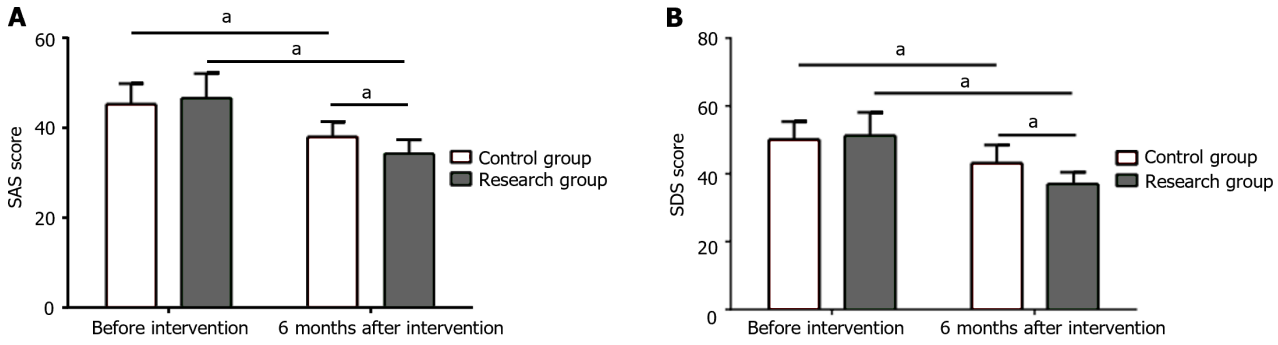

Figure 1 Comparison of Self-Rating Anxiety Scale and Self-Rating Depression Scale scores. A: Comparison of Self-Rating Anxiety Scale scores; B: Comparison of Self-Rating Depression Scale scores. [a]*P* < 0.001. SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale.

FOOTNOTES

Author contributions: Zhang SH and Wu BY designed the research and wrote the first manuscript; Zhang SH, Wang JH, Liu HY, Zhang YX, Lin YL and Wu BY contributed to conceiving the research and analyzing data; Zhang SH and Wu BY conducted the analysis and provided guidance for the research; all authors reviewed and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Therapeutic effect of manual massage on early postpartum rectus abdominis separation and postpartum depression

Yun Chen, Xiao-Yan Sun, Cheng Qian, Xiao-Xing Zhang, Yin-Jian Zhou, Hong-Yun Zhang, Zhen-Wei Xie

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Abstract

BACKGROUND

Rectus abdominis separation (DRA) affects pelvic stability and body image. No studies have explored the effects of manual massage on early postpartum DRA and postpartum depression.

AIM

To analyze the curative effect of massage on early postpartum DRA and its impact on postpartum depression and thus its ability promote the overall psychosomatic rehabilitation of postpartum women.

METHODS

Data were retrospectively collected on 70 primiparous women with postpartum DRA who underwent rehabilitation at the Postpartum Rehabilitation Center of Huzhou Maternal and Child Health Hospital from October 2022 to September 2023. The patients were divided into the Group S (35 cases, biomimetic electrical stimulation treatment) and Group L (35 cases, biomimetic electrical stimulation combined with manual massage treatment). Baseline data, the edinburgh po-

stpartum depression scale (EPDS) score, and the visual analog scale (VAS) scores for rectus abdominis distance, waist circumference, and lower back pain before and after treatment were compared.

RESULTS

No significant differences were found in the baseline data, rectus abdominis distance, waist circumference, and VAS and EPDS scores between the two groups before treatment ($P > 0.05$). After treatment, the distance between rectus abdominis and waist circumference in Group L were significantly smaller than those in Group S ($P < 0.05$). Furthermore, lower back pain (VAS score) and the EPDS score in Group L were significantly lower than those in Group S ($P < 0.05$).

CONCLUSION

Manual massage can significantly reduce early postpartum DRA, waist circumference, and back pain and improve the patient's mental state and postpartum depression.

Key Words: Manual massage; Postpartum; Rectus abdominis muscle separation; Postpartum depression

Core Tip: Postpartum rectus abdominis separation can cause abdominal distension, difficulty in defecation, and pelvic floor dysfunction. It significantly impacts body image and can lead to negative emotions such as anxiety and inferiority complex in women after childbirth, increasing the incidence of postpartum depression. This study describes the ability of massage in reducing the separation of the rectus abdominis muscle, waist circumference, and lower back pain and improving the patient's mental state, which helps lower the risk of postpartum depression.

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INTRODUCTION

Rectus abdominis separation (DRA) is the abnormal separation of the medial edge of the rectus abdominis muscles on both sides of the abdomen. It usually occurs in middle to late pregnancy and postpartum. The main manifestations include abdominal distension, difficulty in defecation, and pelvic floor dysfunction. No uniform diagnostic criteria for postpartum has been established for DRA. Most scholars regard rectus abdominis distance > 2 cm as DRA[1]. DRA usually resolves moderately within 1-8 wk postpartum[2]. However, without any reasonable therapeutic intervention, approximately 39%-70% of DRA cannot recover spontaneously within 6-8 wk postpartum[3], and approximately 39%-45% of DRA cases persist within half a year[4]. The persistence of DRA can lead to various problems, such as pelvic instability, back pain, abdominal wall hernia, and internal organ prolapse[5]. DRA creates an abdominal bulge, which can greatly affect body image and lead to emotional disorders, such as low mood and feelings of inferiority in women with postpartum DRA, which increase the risk of postpartum depression. Postpartum depression is a type of mood disorder experienced after birth characterized by depression and extreme emotional distress. In severe cases, hallucinations or suicidal tendencies can develop[6]. Therefore, postpartum rehabilitation should not be limited to the recovery of DRA, pelvic floor strength, and other physical effects of childbirth. Attention should also be paid to the psychological recovery of postpartum women, in order to achieve the holistic rehabilitation of mind and body. Current conservative treatment methods for postpartum DRA in China mainly include life guidance, abdominal muscle group autonomous training, and bionic electrical stimulation. However, the therapeutic effects are often poor due to nonstandard movements, poor compliance, and intolerance to electrical stimulation[7]. Manual massage is an important part of traditional Chinese medicine with a long history. However, manual massage has only been recently integrated in postpartum rehabilitation. This study investigated the effect of manual massage on early postpartum DRA and postpartum depression to confirm the benefit of traditional Chinese medicine massage in postpartum rehabilitation.

MATERIALS AND METHODS

Patient characteristics

Data were retrospectively collected on 70 primiparous women with postpartum DRA who underwent rehabilitative treatment at the Postpartum Rehabilitation Center of Huzhou Maternal and Child Health Hospital from October 2022 to September 2023. The patients were divided according to the rehabilitation treatment method received into the Group S,

who were treated with biomimetic electrical stimulation, and Group L, who were treated with a combination of bionic electrical stimulation combined and manual massage (n = 35 per group).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) In line with the "expert consensus on the diagnosis and treatment of postpartum DRA" related diagnostic criteria[8], *i.e.*, the pregnant women were 6-8 wk postpartum, lochia has subsided, and the separation distance of rectus abdominis muscle ≥ 2 cm on ultrasound examination; (2) muscle strength of types I and II pelvic floor muscles ≥ grade 3; (3) singleton, full-term pregnancy with no macrosomia; (4) no serious systemic complications, such as postpartum hemorrhage and incision infection; (5) no contraindication of electrical stimulation; and (6) signed informed consent form by the patient and family members.

The exclusion criteria were as follows: (1) Mental disorder or mental retardation; (2) pelvic floor disorders; (3) diagnosis of epilepsy; (4) implanted with a cardiac pacemaker; (5) previous abdominal surgery; (6) intestinal adhesion or congenital abdominal wall dysplasia; (7) long-term cough, constipation, and other diseases that increase abdominal pressure; (8) presence of malignant tumors; (9) severe heart, liver, and kidney dysfunction; and (10) unwilling to cooperate with the treatment or lost to follow-up.

Therapeutic methods

All patients were guided by the rehabilitation physician to undergo independent training that included routine rehabilitation exercises, such as supine leg lifting, kneeling abdominal contraction, kneeling leg extension, flat abdominal contraction, and standing abdominal contraction.

Group S, the conventional rehabilitation exercise group, underwent biomimetic electrical stimulation treatment using a biological stimulation feedback instrument (Nanjing Medland Medical Technology Co., Ltd.; model specification: MLD B4). Each patient was placed in a supine position. Electrode sheets were placed on the external and internal oblique muscles, rectus abdominis, and transversus abdominis on both sides of the abdomen. Electrode wires were used to connect six channels and three loops. Muscle tremor, passive contraction, and comfortable tingling sensation were taken as the standard while considering the patient's tolerance. The best current intensity was then determined. Each stimulation lasted for 30 min. The treatment course was one treatment per day for 10 d. The results were reviewed after 1 course of treatment.

Group L underwent a manual massage in addition to routine rehabilitation exercise and bionic electrical stimulation treatment. Each patient was placed in a supine position and asked to relax the body. The abdomen was exposed while the rest of the body was covered and kept warm. The rehabilitation physician poured an appropriate amount of lavender essential oil to the palm and applied it evenly to the abdomen using the Taiji technique. The abdomen was kneaded 5-8 times, and the pericostal and anterior iliac spine muscles 3-5 times along the direction of the navel. The abdomen was pressed 3-5 times along the navel to the rectus abdominis on both sides. The rectus abdominis was lifted 15 times and the belt vein 8-10 times. The abdomen was encircled, with the Shenque point as the center, and the points of Qimen, Tianshu, and Zhongji were pushed back and forth five times. Point kneading technique was performed according to the Shenshu, Zhongwan, Xiawan, Shenque, Qihai, Guanyuan, Zhongji, Qugu, and Huiyin points. The massage techniques of pressing, kneading, plucking, and rolling were adopted. The acupoints and deep muscle groups were stimulated along the meridian direction of the patient. The muscles on both sides of the waist to the middle were massaged for 20 min each time, The treatment course was one treatment per day for 10 d. The results were reviewed after 1 course of treatment.

Evaluation of therapeutic efficacy indicators

The following indicators were evaluated before and after treatment: (1) Distance between rectus abdominis muscles: The distance between the rectus abdominis muscles was measured by color Doppler ultrasound (Siemens Production; model specification: Sonoline G50). Each patient was placed in a supine position with both knees bent at 90°. The hands were placed on both sides of the body. The ultrasonic probe was used to measure the distance between the rectus abdominis muscles at three sites (3 cm above the umbilicus, in the middle of the umbilicus, and 3 cm below the umbilicus). Each site was measured twice, and the average measurement was obtained; (2) abdominal circumference: The abdominal circumferences at the middle of the umbilicus and at 3 cm above and below the umbilicus were measured using a soft ruler. Each section was measured twice, and the average was obtained; (3) lower back pain: The visual analog scale (VAS) was used to evaluate lower back pain in the patients. The possible total score ranged from 0 to 10 points. A higher score indicated greater pain severity[9]; and (4) postpartum depression: The edinburgh postpartum depression scale (EPDS) was used to evaluate postpartum depression. The scale consists of 10 items with a possible total score ranging from 0 to 30 points. The higher the score, the more severe the depression[10].

Statistical analysis

SPSS 23.0 software was used to analyze and process the data. Count data were expressed as number (percentage). The two groups were compared using the χ^2 test. Normally distributed measurement data were expressed as mean ± SD. Comparisons between the groups were performed using student's t-test. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of baseline data

The differences between Groups S and L in terms of age, body mass index, delivery method, and pelvic floor muscle strength grade were not significant ($P > 0.05$; Table 1).

Comparison of the distance between rectus abdominis muscles

The differences between Groups L and S in the pretreatment distances between the median rectus abdominis, between the rectus abdominis 3 cm above the umbilicus, and between the rectus abdominis 3 cm below the umbilicus in Groups L and S were not significant ($P > 0.05$). However, the posttreatment distances between the median rectus abdominis, between the rectus abdominis 3 cm above the umbilicus, and between the rectus abdominis 3 cm below the umbilicus in Group L were significantly smaller than those in Group S ($P < 0.05$; Table 2 and Figure 1).

Comparison of abdominal circumference indicators

No significant differences were observed between Groups S and L in the abdominal circumferences 3 cm above the umbilicus, in the middle of the umbilicus, and 3 cm below the umbilicus before treatment ($P > 0.05$). However, after treatment, the abdominal circumferences 3 cm above the umbilicus, in the middle of the umbilicus, and 3 cm below the umbilicus in Group L were significantly smaller than those in Group S ($P < 0.05$; Table 3).

Comparison of lower back pain VAS scores

The difference in pretreatment VAS scores for lower back pain between Groups S and L was not significant ($P > 0.05$). However, after treatment, the lower back pain VAS score in Group L was significantly lower than that in Group S ($P < 0.05$; Table 4).

Comparison of postpartum depression scores

The difference in pretreatment EPDS scores between Groups S and L was not significant ($P > 0.05$). However, the posttreatment EPDS score in Group L was significantly lower than that in Group S ($P < 0.05$; Table 5).

DISCUSSION

Physiological changes in the mother during pregnancy, such as elevated progesterone levels and fetal pressure on the uterus, can weaken the elasticity of the skeletal muscle tissue structure and abdominal muscle contraction force, and expand and stretch the bilateral rectus abdominis muscles to both sides, all of which can lead to DRA[11]. The abdominal wall is very important to the human body. If the DRA postpartum cannot be recovered effectively, the abdominal muscles will weaken over time. This muscle weakening has adverse effects on the support of abdominal organs and maintenance of pelvic stability[12]. The long-term persistence of DRA can cause pelvic and lumbar spine injuries and increase lower back pain, which can seriously affect the quality of life and physical and mental health of patients. Therefore, exploring effective treatment methods for early postpartum DRA is of great significance to improving the quality of life postpartum.

Biomimetic electrical stimulation promotes abdominal muscle contraction, increase the excitability of the muscles, enhance muscle strength[13], and encourages the convergence of the rectus abdominis muscle toward the abdominal white line. It is commonly used as passive physical therapy for early postpartum DRA. Traditional Chinese medicine classifies postpartum DRA under the category of "tendon meridian." The disease is located in the abdomen and waist. The abdomen is yin; the waist and back are yang. Treatment should follow the principle of "Yin Ping Yang Mi"[14]. Manual Tuina massage, a traditional Chinese medicine treatment, involves massaging the abdominal muscles through techniques that can promote blood flow, enhance abdominal muscle contraction and elasticity, and maintain the mechanical balance of abdominal muscles. In this study, the distance between the rectus abdominis muscles and abdominal circumference measurements in Group L were significantly smaller than those in Group S after treatment ($P < 0.05$). This indicates that manual massage as supplement to bionic electrical stimulation therapy can further promote recovery from early postpartum DRA. Biomimetic electrical stimulation awakens muscle proprioceptors and enhances the activity level of separated muscle groups. The combination of massage techniques and back and forth massage performed on the acupoints of Qimen, Tianshu, and Zhongji can retrain the corresponding rectus abdominis muscles inside the acupoints, increase their elasticity and strength, and prevent or treat any muscle atrophy. Meanwhile, massage can also improve blood circulation in the arteries and veins on the abdominal wall and thus improve the distribution of nutrients to the rectus abdominis muscle, thereby enhancing the repair of the rectus abdominis muscles to their normal state. Furthermore, during manual massage, acupoints, such as Shangwan-Shenque-Qugu, are fully lifted and pinched, which help dredge meridians, relieve muscle fatigue, increase ligament elasticity, and improve muscle strength. With the resulting increase in abdominal muscle elasticity and tension, the abdominal shape is gradually improved. At the same time, oil deposition in the body is reduced, thereby inhibiting fat accumulation, improving symptoms of abdominal wall relaxation and swelling, and reducing the abdominal circumference.

Pregnancy and childbirth can both lead to widening and weakening of the lumbar tendon, relaxation of the abdominal skin, and sagging and bulging of the midline, which causes instability in the abdominal core and leads to postpartum lower back pain[15]. Studies have shown that the pathological characteristics of lower back pain in patients with

Table 1 Comparison of baseline data, *n* (%)

Baseline data	Group S (*n* = 35)	Group L (*n* = 35)	t/χ^2	*P* value
Age (yr)	28.20 ± 3.76	29.66 ± 3.04	1.786	0.078
Body mass index (kg/m^2)	23.05 ± 2.78	22.76 ± 2.75	0.439	0.662
Delivery method			0.057	0.811
Cesarean section	17 (48.57)	16 (45.71)		
Spontaneous labor	18 (51.43)	19 (54.29)		
Pelvic floor muscle strength grading			0.473	0.789
Level 3	10 (28.57)	11 (31.43)		
Level 4	19 (54.29)	20 (57.14)		
Level 5	6 (17.14)	4 (11.43)		

Table 2 Comparison of distance between rectus abdominis muscles

Group	*n*	3 cm above umbilicus		Navel midline		3 cm below umbilicus	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group S	35	3.24 ± 0.51	1.86 ± 0.24	3.75 ± 0.66	2.01 ± 0.33	2.23 ± 0.56	1.71 ± 0.32
Group L	35	3.23 ± 0.93	1.65 ± 0.31	3.67 ± 1.09	1.78 ± 0.18	2.43 ± 0.66	1.55 ± 0.19
t value		0.056	3.169	0.371	3.777	1.367	2.486
P value		0.996	0.002	0.711	< 0.001	0.176	0.015

Table 3 Comparison of abdominal circumference index

Group	*n*	3 cm above umbilicus		Navel midline		3 cm below umbilicus	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group S	35	83.83 ± 7.08	82.86 ± 7.67	85.73 ± 7.93	84.43 ± 7.73	87.26 ± 7.41	86.17 ± 7.84
Group L	35	83.29 ± 7.26	79.60 ± 4.75	84.39 ± 7.36	80.90 ± 5.10	86.40 ± 7.53	82.79 ± 5.43
t value		0.315	2.138	0.733	2.255	0.482	2.097
P value		0.754	0.036	0.466	0.027	0.632	0.039

Table 4 Comparison of lower back pain visual analog scale scores

Group	*n*	Lower back pain VAS score	
		Before treatment	After treatment
Group S	35	2.57 ± 1.29	1.26 ± 0.74
Group L	35	2.51 ± 1.36	0.77 ± 0.59
t value		0.19	3.063
P value		0.85	0.003

VAS: Visual analog scale.

postpartum DRA are mainly caused by abdominal muscle spasm and myofascial incarceration[16]. Tuina can promote analgesic effects by stimulating different levels of targets[17]. Smith *et al*[18] reported that manual massage can alleviate the pain of childbirth. In the present study, the lower back pain VAS score in Group L was significantly lower than that in Group S ($P < 0.05$), indicating the enhanced therapeutic effect of manual massage and biomimetic electrical stimulation therapy on lower back pain. This may be related to the therapeutic effects brought about by manual massage through dredging meridians and preserving tendons. Therefore, bionic electrical stimulation therapy combined with manual

Table 5 Comparison of Edinburgh postpartum depression scale scores

Group	*n*	EPDS score	
		Before treatment	After treatment
Group S	35	9.86 ± 2.37	9.03 ± 1.28
Group L	35	9.92 ± 2.41	8.24 ± 1.06
t value		0.105	2.812
P value		0.917	0.006

EPDS: Edinburgh postpartum depression scale.

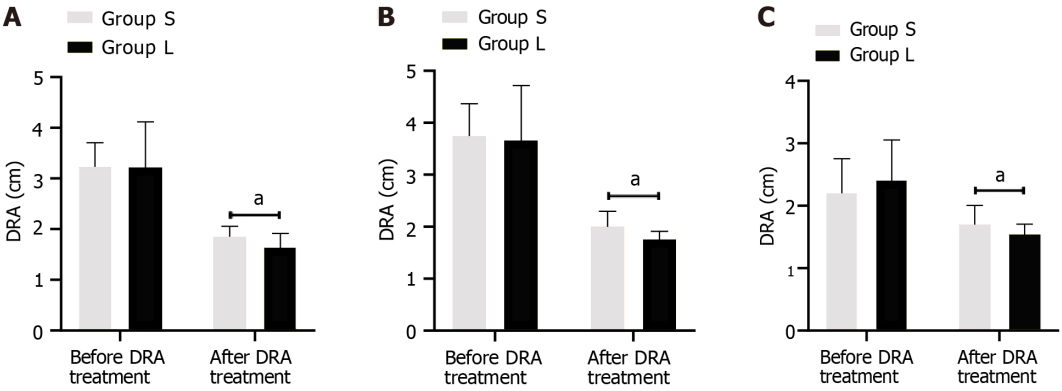

Figure 1 Comparison of separation distance between rectus abdominis muscles. A: Rectus abdominis distance 3 cm above the umbilicus before and after treatment; B: Distance between the midumbilical rectus abdominis before and after treatment; C: Rectus abdominis distance 3 cm below the umbilicus before and after treatment. [a]*P* < 0.05 *vs* between Groups S and L. DRA: Rectus abdominis separation.

massage can more effectively promote the healing of inflammation- and pain-causing substances in the body. Meanwhile, this combination treatment can effectively promote abdominal blood circulation, improve muscle tone, reduce stimulation to the lumbar nerves, and relieve symptoms of lower back pain.

The changes in abdominal appearance caused by postpartum DRA can have varying degrees of impact on the emotions of postpartum women, which mainly manifest as lack of interest, low emotions, and depression, among others [19]. This may be related to contemporary women's pursuit of an ideal body shape. Postpartum DRA induces negative emotions, which will affect patients' participation in postpartum rehabilitation, which in turn negatively affects the repair of the rectus abdominis muscles, such as further aggravation of the separation and even injury, forming a vicious cycle [20]. In the present study, the posttreatment EPDS score in the Group L was significantly lower than that in the Group S ($P < 0.05$). This may be related to the relaxation that manual massage can provide. Relaxation can alleviate the postpartum emotional state. Stimulation of the sensory nerve fibers on the skin can relax tense muscles, creating a calming experience. These benefits positively affect mood and improve the overall mental state, in addition to the physical benefits. Manual massage can also improve early postpartum DRA and abdominal circumference indicators and alleviate lower back pain. These positive holistic effects will also help improve the depressive mood in postpartum patients. Kianpour *et al*[21] found that lavender essential oil can relieve postpartum depression. This is the rationale behind the massage oil used in this study. Typically, essential oil is applied to the patient's abdomen, and Tai Chi technique is used to massage the abdomen 5-8 times. This technique helps release lavender essential oil molecules, allowing them to float in the air, promoting nasal inhalation. The effect on the limbic system of the brain (the amygdala and hippocampus) in turn has a psychological outcome[22] that promotes positive emotions and alleviates patient anxiety and depression.

This study has some limitations. First, the efficacy of biomimetic electrical stimulation therapy combined with manual massage is significant, but whether long-term DRA will recur remains to be confirmed. Second, the single-center design and small sample size limit the generalizability of the results. Further larger-scale sample involving multiple centers are needed to validate the conclusions derived in this study.

CONCLUSION

Manual massage has a significant therapeutic effect on early postpartum DRA. Its combination with biomimetic electrical stimulation therapy effectively reduced DRA, waist circumference, and lower back pain. Furthermore, manual massage promoted relaxation, which can alleviate the physical and mental states and improve postpartum depression.

FOOTNOTES

Author contributions: Chen Y and Sun XY contributed equally to this work and are co-first authors; Chen Y and Sun XY designed the research and wrote the first manuscript; Chen Y, Sun XY, Qian C, Zhang XX, Zhou YJ, Zhang HY and Xie ZW contributed to conceiving the research and analyzing data; Chen Y, Sun XY and Xie ZW conducted the analysis and provided guidance for the research; all authors reviewed and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Differences in insomnia-related self-reported outcomes among elderly hospitalized patients

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Abstract

BACKGROUND

Insomnia is among the most common sleep disorders worldwide. Insomnia in older adults is a social and public health problem. Insomnia affects the physical and mental health of elderly hospitalized patients and can aggravate or induce physical illnesses. Understanding subjective feelings and providing reasonable and standardized care for elderly hospitalized patients with insomnia are urgent issues.

AIM

To explore the differences in self-reported outcomes associated with insomnia among elderly hospitalized patients.

METHODS

One hundred patients admitted to the geriatric unit of our hospital between June 2021 and December 2021 were included in this study. Self-reported symptoms were assessed using the Athens Insomnia Scale (AIS), Generalized Anxiety Disorder Scale-7 (GAD-7), Geriatric Depression Scale-15 (GDS-15), Memorial University of Newfoundland Scale of Happiness (MUNSH), Barthel Index Evaluation (BI), Morse Fall Scale (MFS), Mini-Mental State Examination, and the Short Form 36 Health Survey Questionnaire (SF-36). Correlation coefficients were used to analyze the correlation between sleep quality and self-reported symptoms. Effects of insomnia was analyzed using Logistic regression analysis.

RESULTS

Nineteen patients with AIS ≥ 6 were included in the insomnia group, and the incidence of insomnia was 19% (19/100). The remaining 81 patients were assigned to the non-insomnia group. There were significant differences between the two groups in the GDA-7, GDS-15, MUNSH, BI, MFS, and SF-36 items ($P < 0.05$). Patients in the insomnia group were more likely to experience anxiety, depression, and other mental illnesses, as well as difficulties with everyday tasks and a greater risk of falling ($P < 0.05$). Subjective well-being and quality of life were poorer in the insomnia group than in the control group. The AIS scores positively correlated with the GAD-7, GDS-15, and MFS scores in elderly hospitalized patients with insomnia ($P < 0.05$). Logistic regression analysis showed that GDS-15 ≥ 5 was an independent risk factor for insomnia in elderly hospitalized patients ($P < 0.05$).

CONCLUSION

The number of self-reported symptoms was higher among elderly hospitalized patients with insomnia. Therefore, we should focus on the main complaints of patients to meet their care needs.

Key Words: Elderly hospitalized patients; Insomnia; Self-reported outcomes; Symptoms; Subjective feelings; Correlation

Core Tip: Face-to-face interviews were conducted with 100 elderly hospitalized patients. Elderly hospitalized patients had higher rates of insomnia symptoms. Insomnia in elderly hospitalized patients positively correlated with anxiety, depression, and fall risk. Depression was also found to be an independent risk factor for insomnia in elderly hospitalized patients.

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INTRODUCTION

According to the seventh national population census conducted in 2020, there were 264.02 million people, 60 years of age or older in China, making up 18.70% of the total population, and this proportion is only expected to grow. An important part of building a "Healthy China" is ensuring that the older population is cared for, both physically and psychologically, and that their quality of life is enhanced. Insomnia, a common sleep disorder in older adults, not only increases the risk of cardiovascular and cerebrovascular diseases, diabetes, and neurodegenerative diseases, but also damages physical and mental health (MH)[1-3]. Insomnia may exacerbate pre-existing conditions in elderly hospitalized patients and severely reduce their quality of life. It is an important part of clinical nursing work to focus on and improve the quality of sleep of elderly hospitalized patients.

Recently, an increasing number of researchers have acknowledged that patients should play an active role in managing their own health[4]. The study of patient-reported outcomes (PROs) originated in the 1970s and refers to health-related information obtained directly from patients without any interpretation by others[5]. PROs may be gathered *via* patient interviews and questionnaires, with patients' subjective experiences being used as a foundation for evaluating symptoms, and self-reported indicators of disease and treatment outcomes such as symptom burden, psychological sentiments, functional status, quality of life, and others are the major focus of the assessment[6]. Self-reported outcome measurements from patients considerably enhance treatment quality and comfort[7,8]. Therefore, this study applied PROs to elderly hospitalized patients, aiming to understand the variations in insomnia-related self-reported outcomes of these patients and provide a theoretical foundation for implementing precision care.

MATERIALS AND METHODS

Research object

One hundred elderly hospitalized patients in the geriatric department of our hospital were selected for face-to-face interviews between June 2021 and December 2021. The inclusion criteria were as follows: (1) Age ≥ 60 years old, with good orientation to time, place, and people; (2) able to communicate verbally; and (3) volunteered to participate in this study. The exclusion criteria were as follows: (1) Severe sleep-affecting diseases, (2) major personal or family events in the past 2 months, and (3) severe cognitive impairment or inability to self-report outcomes. There were 57 males (57%) and 43 females (43%), with an average age of 71.8 ± 7.17 years. This study was approved by the Hospital Ethics Committee (No. 2021-K058-01), and all participants signed an informed consent form.

General information

A self-designed scale was used in the general information questionnaire to examine the general situation of elderly patients, including age, sex, body mass index (BMI), place of residence, living arrangements, monthly income, marital status, level of education, occupation, smoking, drinking, and physical activity.

PRO measurement tools

Insomnia symptom scale: Self-evaluation of sleep disturbances was documented using the Athens Insomnia Scale (AIS) [9], which was created in 2000 in accordance with the International Classification of Diseases (10th edition) standards. The evaluation time of the scale was 1 month. The higher the score, the worse the sleep quality, and a total score of 6 points or more indicates a high probability of insomnia (sensitivity 93%, specificity 85%)[10]. According to a previous study, the AIS may be used as a screening tool to accurately diagnose insomnia because of its high sensitivity and specificity[11].

Psychological feeling scale: The Generalized Anxiety Disorder Scale-7 (GAD-7)[12] was used to assess the degree of generalized anxiety. The scale contains seven items, with a total range of 0–21. A score less than or equal to 4 indicates no anxiety symptoms, while 5, 10, and 15 correspond to mild, moderate, and severe anxiety, respectively[13]. The Geriatric Depression Scale-15 (GDS-15)[14] was used to assess the degree of generalized depression. The scale has 15 entries, each with two answers: "yes" (1 score) or "no" (0 points). A score of 0–4 is considered no depression, 5–10 indicates mild depression, and 11–15 indicates major depression[15]. The Memorial University of Newfoundland Scale of Happiness (MUNSH) was used to measure subjective well-being. The scale contains 24 entries, of which five reflect positive emotions (PA), five reflect negative emotions (NA), seven reflect positive experiences (PE), and seven reflect negative experiences (NE). The total MUNSH score was calculated as follows: Total happiness = PA – NA + PE – NE + 24, ranging from 0 to 48[16].

Functional status scale: The Barthel index (BI)[17] is an ordinal scale used to measure a patient's ability of daily living, including eating, bathing, and dressing, using a 10 point scale for each item. A perfect score is 100, ranging from 0 (totally dependent) to 100 (totally independent). A score of less than 100 indicates impaired activities of daily living[18]. The Morse Fall Scale (MFS)[19] was used to measure fall risk, including fall history, disease diagnosis, walking, intravenous fluid, gait, and cognitive status, with a maximum score of 125. A score < 25 indicates low fall risk, 25–45 indicates medium fall risk, and > 45 indicates high fall risk[20]. The Mini-Mental State Examination (MMSE)[21] includes five cognitive aspects: Orientation, memory, attention/computation, memory, and language, with a total score of 30. Scores of less than 24 (> 6 years of education or intermediate or above), 20 (< 6 years of education), and 17 (illiterate) were considered cognitively impaired[22].

Health-related quality of life scale: The Short Form 36 Health Survey Questionnaire (SF-36) has eight dimensions: Physical function (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and MH, each of which is scored on a scale of 100, with scores proportional to quality of life[23].

Quality control

Quality control was performed as follows: (1) Using uniform inclusion and exclusion criteria; (2) through face-to-face interviews, using a unified scale for self-reporting by patients; (3) data collection by regular personnel; (4) provision of relevant training to all survey members before the survey, such as insomnia-related knowledge, unified guidance, scale content and precautions; (5) surveys conducted in a small area in advance to observe the rationality and operability of the questionnaire; (6) before data entry, training and guidance was provided to entry personnel, and all data was processed according to the unified scoring standard; (7) before data analysis, coding and data entry were checked for errors; and (8) two-person entry verification was implemented during to ensure the reliability of the data.

Statistical analysis

Data were analyzed using IBM SPSS Statistics software (version 23.0; IBM, Armonk, NY, United States). Normally distributed continuous variables are expressed as mean ± SD, using the independent-samples t-test. Continuous variables with a non-normal distribution were represented as median and quartile [M (Q_{25}, Q_{75})], and non-parametric tests were used. Categorical variables were expressed in terms of frequency and composition ratio [*n* (%)], and the chi-squared test was used for statistical difference analysis. The correlation between insomnia and psychological status, daily living ability, and quality of life scores was analyzed using the double correlation variable and Spearman correlation coefficient when the data did not fit a normal distribution. Logistic regression analysis was used to analyze the risk factors for insomnia. All statistical analyses were performed using two-sided tests, and $P < 0.05$ was considered statistically significant.

RESULTS

Insomnia status and sociodemographic characteristics

Of the 100 elderly hospitalized patients, 19 were included in the insomnia group and the remaining 81 were included in the non-insomnia group. Cohabitation and marriage status were significantly different between the two groups ($P < 0.05$), but there were no significant differences in age, sex, BMI, place of residence, monthly income, education level, profession, drinking, smoking, or physical activity ($P > 0.05$; Table 1).

Table 1 Sociodemographic characteristics of elderly hospitalized patients, *n* (%)

Items	Insomnia (*n* = 19)	Non- insomnia (*n* = 81)	*P* value
Age (yr, mean ± SD)	74.68 ± 7.95	71.12 ± 6.86	0.051
Sex			0.669
Male	10 (52.63)	47 (58.02)	
Female	9 (47.37)	34 (41.98)	
BMI (kg/m^2, mean ± SD)	24.22 (20.05, 26.42)	22.32 (20.7, 25.44)	0.524
Place of residence			0.999
Town	2 (10.53)	7 (8.64)	
Other	17 (89.47)	74 (91.36)	
Cohabitation			0.032
Living with children	9 (47.37)	29 (35.80)	
Living with spouse	6 (31.58)	48 (59.26)	
Living alone	4 (21.05)	4 (4.94)	
Monthly income			0.427
≥ 2000	12 (63.16)	43 (53.09)	
2000	7 (36.84)	38 (46.91)	
Marital status			0.041
Married	12 (63.16)	70 (86.42)	
Divorced/widowed	7 (36.84)	11 (13.58)	
Education level			0.999
≤ 9 yr	15 (78.95)	64 (79.01)	
9 yr	4 (21.05)	17 (20.99)	
Profession			0.495
Public and business personnel	7 (36.84)	18 (22.22)	
Farmer	6 (31.58)	35 (43.21)	
Laborer	5 (26.32)	26 (32.10)	
Other	1 (5.23)	2 (2.47)	
Smoking			0.234
Yes	0	10 (12.35)	
No	19 (100)	71 (87.65)	
Drinking			0.185
Yes	2 (10.53)	23 (28.40)	
No	17 (89.47)	58 (71.60)	
Physical exercise			0.951
Yes	10 (52.63)	42 (51.85)	
No	9 (47.37)	39 (48.15)	

BMI: Body mass index.

Psychological feeling

There were eight patients in the insomnia group and seven in the non-insomnia group with GDA-7 ≥ 5. The incidence of anxiety in the insomnia group was significantly higher than that in the non-insomnia group [42.11% (8/19) *vs* 8.64% (7/81), $P < 0.05$]. There were 11 and 8 cases in the insomnia and non-insomnia groups with GDS-15 ≥ 5, respectively. The incidence of depression in the insomnia group was significantly higher than that in the non-insomnia group [57.89% (11/

19) *vs* 9.88% (8/81), $P < 0.05$]. The MUNSH scores in the insomnia group were significantly lower than those in the non-insomnia group ($P < 0.05$; Figure 1A).

Functional status

There were 11 and 25 patients in the insomnia and non-insomnia groups, respectively, with BI < 100. The incidence of impaired activities of daily living in the insomnia group was significantly higher than that in the non-insomnia group [57.89% (11/19) *vs* 30.86% (25/81), $P < 0.05$]. In the insomnia group, four patients had a low fall risk, 11 had a medium fall risk, and four had a high fall risk. In the non-insomnia group, 44 patients had a low fall risk, 32 had a medium fall risk, and five had a high fall risk. The severity of fall risk was higher in the insomnia group than in the non-insomnia group ($P < 0.05$; Figure 1B). There were no significant differences in MMSE scores between groups ($P > 0.05$; Figure 1C).

Health-related quality of life

There were no significant differences in BP, SF, RE, MH between the two groups ($P > 0.05$). There were significant differences in the PF, RP, GH, VT, and total scores between the two groups ($P < 0.05$; Table 2).

Correlation analysis of insomnia in elderly hospitalized patients

The AIS, GAD-7, GDS-15, BI, MFS, MMSE, and SF-36 scores in the insomnia group are shown in Table 3. AIA scores positively correlated with GAD-7, GDS-15, and MFS scores ($P < 0.05$; Table 4).

Multivariate analysis of insomnia in elderly hospitalized patients

Statistically significant indicators in the univariate analysis were taken as independent variables (Table 5) and insomnia as a dependent variable (0 = no, 1 = yes) in the logistic regression equation. Logistic regression analysis showed that GDS-15 ≥ 5 was an independent risk factor for insomnia in elderly hospitalized patients (Table 6).

DISCUSSION

The incidence of insomnia is increasing, with up to one in three adults worldwide suffering from this condition[24]. More than 300 million people in China had sleep disorders in 2021, and the adult insomnia rate is as high as 38.2%, according to the White Paper on China's National Healthy Sleep in 2022[25]. According to international studies, the incidence of insomnia symptoms among older adults ranges from 30%–48%[26]. The physiological activities of the body function decline with increasing age[27], and coupled with the impact of disease, the sleep quality of elderly patients is generally low, but their need for sleep is not reduced. Therefore, attention should be paid to the prevention and treatment of insomnia in elderly patients.

This study found that the incidence of insomnia symptoms among elderly hospitalized patients was 19%. Xiao *et al*[28] included 451 elderly patients in a geriatric unit and found that the incidence of insomnia was approximately 36.59% (165/451), which was higher than the results of this study and may be related to the different inclusion criteria. Their study included elderly patients aged > 65 years, including both outpatients and inpatients. In this study, elderly patients who lived alone, were divorced, or widowed had a high incidence of insomnia, which is consistent with the research results of Ma *et al*[29], which may be due to the higher level of stress brought about by living alone and marital change. Therefore, attention should be paid to screening for insomnia in the above population, strengthening their sleep care, and developing reasonable intervention measures.

In this study, the incidence of anxiety and depression in elderly hospitalized patients with insomnia was significantly higher than that in those without insomnia symptoms, and patients with insomnia had significantly lower subjective well-being than those without insomnia. In addition, correlation analysis showed that insomnia was closely related to anxiety and depression, and logistic regression analysis showed that depression was a risk factor for insomnia in elderly hospitalized patients. While the mechanisms underlying insomnia, anxiety, and depression in older adults are still not fully understood, several studies have shown that insomnia in older adults can be accompanied by anxiety, depression, and other psychological conditions[30-32]. A cross-sectional study also showed that depression is a risk factor for insomnia in older adults[33]. Based on this data, it is recommended to combine the assessment and treatment of insomnia, anxiety, depression, and cognitive function in elderly hospitalized patients and focus on the psychological symptoms and cognitive function of elderly patients while performing sleep monitoring. Further identification of depression, anxiety, other NA, and cognitive function impairments is necessary, particularly for older patients who already have insomnia. At the same time, targeted interventions should be provided as early as possible, with a focus on MH education for older patients with insomnia to prevent or delay its further occurrence and development.

This study found that elderly inpatients with insomnia also have functional deficiencies in daily activities and a high risk of falling, and insomnia is positively correlated with falling risk. Takada *et al*[34] noted that the number of sleepless nights can predict the risk of falls in older adults, which may be related to sleep disturbances, unsteady gait, and poor balance. Our study did not establish a cause-and-effect relationship between insomnia and the risk of falling. Therefore, elderly inpatients should pay attention to their daily activities while reducing their symptoms of insomnia, be provided assistance as necessary, pay attention to patient safety, and avoid falling.

In terms of health-related quality of life, this study demonstrated that elderly inpatients with insomnia had worse physical quality of life, physiological function, physiological role, overall health, and VT. This is consistent with a report by Wang *et al*[35] in which patients with insomnia had a low quality of life. Therefore, we focused on the life care of elderly hospitalized patients with insomnia, starting with physiology and psychology, and effective insomnia treatment

Table 2 Differences in the self-reported outcomes of health-related quality of life among elderly hospitalized patients

Item	Insomnia group (*n* = 19)	Non-insomnia group (*n* = 81)	*P* value
PF [score, M (Q25,Q75)]	45.00 (5.00, 70.00)	70.00 (40.00, 87.50)	0.016
RP [score, M (Q25,Q75)]	0 (0, 25.00)	50.00 (0, 100.00)	0.016
BP [score, M (Q25, Q75)]	62.00 (52.00, 100.00)	100.00 (62.00, 100.00)	0.122
GH [score, M (Q25, Q75)]	52.00 (25.00, 70.00)	65.00 (50.00, 76.00)	0.035
VT [score, M (Q25, Q75)]	50.00 (25.00, 85.00)	70.00 (55.00, 85.00)	0.041
SF [score, M (Q25, Q75)]	62.50 (25.00, 87.50)	75.00 (50.00, 100.00)	0.079
RE [score, M (Q25, Q75)]	100.00 (0, 100.00)	100.00 (0, 100.00)	0.381
MH [score, M (Q25, Q75)]	72.00 (60.00, 92.00)	84.00 (70.00, 92.00)	0.192
SF-36 (score, mean ± SD)	419.58 ± 207.95	541.99 ± 178.45	0.011

PF: Physiological function; RP: Role-physiological; BP: Body pain; GH: General health; VT: Vitality; SF: Social function; RE: Role-emotional; MH: Mental health; SF-36: Short form 36 health survey questionnaire.

Table 3 Scores of each scale in the insomnia group

Item	Scores
AIS [score, M (Q25, Q75)]	10.00 (8.00, 12.00)
GAD-7 [score, M (Q25, Q75)]	1.00 (1.00, 2.00)
GDS-15 (score, mean ± SD)	5.16 ± 2.97
MUNSH [score, M (Q25, Q75)]	40.00 (24.00, 44.00)
BI [score, M (Q25, Q75)]	95.00 (70.00, 100.00)
MFS [score, M (Q25, Q75)]	35.00 (25.00, 45.00)
MMSE [score, M (Q25, Q75)]	26.00 (22.00, 29.00)
SF-36 (score, mean ± SD)	419.58 ± 207.95

AIS: Athens insomnia scale; GAD-7: Generalized anxiety disorder scale-7; GDS-15: Short geriatric depression scale-15; MUNSH: Memorial University of Newfoundland scale of happiness; BI: Barthel index; MFS: Morse falls scale; MMSE: Mini-mental state examination; SF-36: Short form 36 health survey.

Table 4 Correlation analysis of sleep quality in elderly hospitalized patients with insomnia

Item	AIS score	
	r	*P* value
GAD-7 score	0.470	0.042
GDS-15 score	0.459	0.048
MUNSH score	-0.185	0.448
BI	-0.095	0.698
MFS score	0.743	< 0.001
MMSE score	-0.414	0.078
SF-36 score	-0.324	0.176

AIS: Athens insomnia scale; GAD-7: Generalized anxiety disorder scale-7: GDS-15, Short geriatric depression scale-15; MUNSH: Memorial University of Newfoundland scale of happiness; BI: Barthel index; MFS: Morse Falls Scale; MMSE: Mini-mental state examination; SF-36: Short form 36 health survey.

Table 5 Assignment condition

Item	Assignment
Cohabitation	1: Living with children; 2: Living with spouse; 3: Living alone
Marital status	1: Married; 2: Divorced/widowed
GAD-7	1: Score < 5; 2: Score ≥ 5
GDS-15	1: Score < 5; 2: Score ≥ 5
MUNSH	Original input
BI	1: Score < 100; 2: Score of 100
MFS	1: Score < 25; 2: Score 25-45; 3: Score 45
SF-36	Original input

GAD-7: Generalized anxiety disorder scale-7; GDS-15: Short geriatric depression scale-15; MUNSH: Memorial University of Newfoundland scale of happiness; BI: Barthel index; MFS: Morse falls scale; SF-36: Short form 36 health survey questionnaire.

Table 6 Logistic regression analysis of insomnia in elderly hospitalized patients

Item	B	SE	Wald	*P* value	OR (95%CI)
Cohabitation	-0.252	0.480	0.275	0.600	0.777 (0.303-1.993)
Marital status	0.911	0.775	1.381	0.240	2.487 (0.544-11.364)
GAD-7	1.437	0.944	2.319	0.128	4.209 (0.662-26.766)
GDS-15	1.821	0.737	6.103	0.013	6.177 (1.457-26.189)
MUNSH	-0.002	0.040	0.003	0.959	0.998 (0.923-1.079)
BI	-0.682	0.921	0.549	0.459	0.505 (0.083-3.075)
MFS	0.342	0.657	0.272	0.602	1.408 (0.389-5.103)
SF-36	0.001	0.003	0.231	0.631	1.001 (0.995-1.008)

GAD-7: Generalized anxiety disorder scale-7; GDS-15: Short geriatric depression scale-15; MUNSH: Memorial University of Newfoundland scale of happiness; BI: Barthel index; MFS: Morse falls scale; SF-36: Short form 36 health survey questionnaire; OR: Odds ratio.

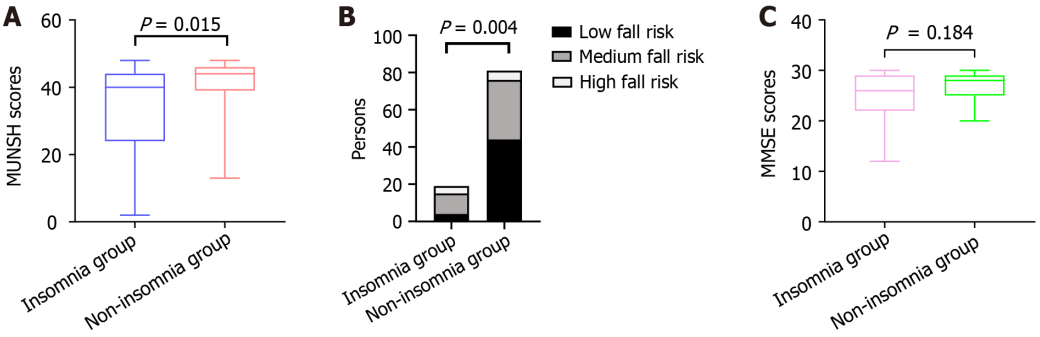

Figure 1 Comparison between groups. A: Comparison of Memorial University of Newfoundland scale of happiness scores between groups; B: Comparison of fall risk between groups; C: Comparison of mini-mental state examination scores between groups. MUNSH: Memorial University of Newfoundland scale of happiness; MMSE: Mini-mental state examination.

to improve their health-related quality of life.

However, this study has certain limitations. First, all information was gathered through patient self-reports. The AIS was created in accordance with the International Classification of Diseases (10th edition) standard, and the relevant scales were used in previous studies; however, the study did not adhere to the guidelines of the International Classification of Sleep Disorders[36] to assess insomnia and objective sleep measurement was not performed. Secondly, this was a cross-sectional study. We were unable to determine whether there was a connection between insomnia and psychosomatic disorders, and further prospective studies are required to confirm this causal link. Finally, this study considered the

differences in sociodemographic factors, psychological feelings, functional status, and health-related quality of life of patients but did not consider the differences in the diseases of the patients.

CONCLUSION

The findings of this study demonstrate that insomnia significantly affects the psychological and functional states of elderly hospitalized patients, which eventually results in a reduction in their health-related quality of life. Therefore, more attention should be paid to the sleep conditions of elderly hospitalized patients, screening and identifying patients with insomnia early, taking multiple measures to relieve insomnia symptoms, and improving quality of life.

FOOTNOTES

Author contributions: Ding X designed and performed the research and wrote the paper; Sun DY designed the research and supervised the report; Qi LX designed the research and contributed to the analysis.

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ORIGINAL ARTICLE

Observational Study

Interaction between catechol-O-methyltransferase Val/Met polymorphism and cognitive reserve for negative symptoms in schizophrenia

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Abstract

BACKGROUND

Cognitive reserve (CR) and the catechol-O-methyltransferase (*COMT*) Val/Met polymorphism are reportedly linked to negative symptoms in schizophrenia. However, the regulatory effect of the *COMT* genotype on the relationship between CR and negative symptoms is still unexamined.

AIM

To investigate whether the relationship between CR and negative symptoms could be regulated by the *COMT* Val/Met polymorphism.

METHODS

In a cross-sectional study, 54 clinically stable patients with schizophrenia underwent assessments for the *COMT* genotype, CR, and negative symptoms. CR was estimated using scores in the information and similarities subtests of a short form of the Chinese version of the Wechsler Adult Intelligence Scale.

RESULTS

COMT Met-carriers exhibited fewer negative symptoms than Val homozygotes. In the total sample, significant negative correlations were found between negative symptoms and information, similarities. Associations between information,

similarities and negative symptoms were observed in Val homozygotes only, with information and similarities showing interaction effects with the *COMT* genotype in relation to negative symptoms (information, β = -0.282, 95%CI: -0.552 to -0.011, P = 0.042; similarities, β = -0.250, 95%CI: -0.495 to -0.004, P = 0.046).

CONCLUSION

This study provides initial evidence that the association between negative symptoms and CR is under the regulation of the *COMT* genotype in schizophrenia.

Key Words: Catechol-O-methyltransferase Val/Met polymorphism; Cognitive reserve; Crystallized intelligence; Negative symptoms; Schizophrenia

Core Tip: Cognitive reserve (CR) and the catechol-O-methyltransferase (*COMT*) Val/Met polymorphism are reportedly linked to negative symptoms, which are a core clinical manifestation of schizophrenia. However, the regulatory effect of the *COMT* genotype on the relationship between CR and negative symptoms is unclear. In this study, *COMT* Met-carriers exhibited fewer negative symptoms than Val homozygotes. Information and similarities showed interaction effects with the *COMT* genotype in terms of negative symptoms. This preliminary study shows that the association between negative symptoms and CR may be under the regulation of the *COMT* genotype in schizophrenia.

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INTRODUCTION

Negative symptoms are a core clinical manifestation of schizophrenia, encompassing blunted affect, alogia, apathy, anhedonia, and avolition[1]. Negative symptoms and cognitive deficits are the most critical determinants in the functional outcome and overall quality of life in schizophrenia[2,3]. Furthermore, negative symptoms have been documented as mediators in the influence of cognitive impairments on functional outcomes[4]. Currently, both pharmacological and non-pharmacological interventions show limited efficacy in treating negative symptoms[5-7]. It is essential to identify the influential factors of negative symptoms to develop individualized and comprehensive intervention strategies for patients with schizophrenia.

Cognitive reserve (CR) is frequently reported as a predictor of negative symptoms in cross-sectional and longitudinal studies[8-11]. CR refers to the ability to buffer the effects of illness through pre-existing and compensatory cognitive processes[12]. It is typically assessed using socio-behavioral measures, including intelligence quotient (IQ), educational level, occupational attainment, and leisure activity participation[13,14]. Apart from affecting negative symptoms, CR can also mitigate the adverse effects of exaggerated structural brain deterioration and disease relapse on neurocognitive function while concurrently enhancing psychosocial functioning[15-20]. The relationship between CR and negative symptoms may be even more pronounced in more severe pathological states[21,22].

Standardized and unified assessment tools are lacking in terms of assessing CR. Although educational level is the most commonly used indicator[12], it is a static measure that reflects learning and cognitive activities during a specific period in early life. By contrast, crystallized intelligence refers to the breadth and depth of knowledge and information that a person acquires over their lifetime[23]. Thus, measures of crystallized intelligence are dynamic and can capture the effects of continuous learning, thereby making them more suitable as alternative indicators of CR[24,25].

Dopamine activity in the prefrontal cortex plays a vital role in regulating negative symptoms in schizophrenia[26]. The catechol-O-methyltransferase (*COMT*) enzyme deactivates dopamine[27]. The *COMT* Val/Met polymorphism is a key genetic factor affecting the activity variation of the eponymous enzyme. Val homozygotes have approximately 40% higher enzyme activity in the prefrontal cortex than Met/Met carriers, potentially leading to lower levels of prefrontal dopamine signaling[28]. Therefore, the *COMT* genotype may be a remarkable factor influencing negative symptoms[29-31], as evidenced by studies that reported increased levels of negative symptoms in Val homozygotes[29].

To date, no study has been conducted on the interaction effects of the *COMT* genotype with CR in terms of negative symptoms. We hypothesized that the association between CR and negative symptoms would be regulated by the *COMT* genotype. Specifically, the correlation between CR and negative symptoms could be stronger in Val homozygotes with relatively more severe pathological features. A cross-sectional study was conducted among stable patients with schizophrenia to test this hypothesis. In this study, CR was primarily estimated by crystallized intelligence.

MATERIALS AND METHODS

Subjects

All data were derived from the baseline dataset of a randomized, controlled, double-blind clinical trial. The trial was conducted from September 2021 to May 2023 at Beijing Anding Hospital in China. The trial was approved by the Ethics Committee of Beijing Anding Hospital (No. 2020-70), and it was registered in the Chinese Clinical Trial Registry (ChiCTR2000038961). The participants in the trial were clinically stable outpatients or community-dwelling individuals with schizophrenia, aged between 18 and 50 years, with an IQ score above 70, and a minimum of 8 years of education. The primary exclusion criteria included a history of severe physical illness such as craniocerebral trauma or infection, brain tumor, cerebrovascular disease, and epilepsy according to patient self-description; as well as a history of alcohol or substance use disorders during the past 6 months. Sixty participants were enrolled at baseline, of which 54 completed testing for single-nucleotide polymorphisms for the cross-sectional analysis of this study.

Assessment tools

The diagnoses of schizophrenia and alcohol or substance use disorders were based on the DSM-5 criteria utilizing the Mini International Neuropsychiatric Interview (version 7.0.2). Clinical symptoms were assessed using the Positive and Negative Syndrome Scale, which includes a positive subscale for positive symptoms, a negative subscale for negative symptoms, and the general psychopathology subscale for general symptoms[32]. IQ was evaluated using a short form of the Chinese version of the Wechsler Adult Intelligence Scale (WAIS-RC), consisting of four subtests[33]. The information and similarities subtests primarily reflect crystallized intelligence, whereas the picture completion and block design subtests are designed to measure fluid intelligence which is the capacity to think logically and solve problems in novel situations. Together, these four subtests represent a rough measure of general ability[33,34].

Genotyping

Whole blood was utilized for DNA extraction. The rs4680 locus sequence was probed for the *COMT* Val/Met polymorphism. Genotypes were identified by polymerase chain reaction amplification, incorporation of terminator nucleotides and subsequent agarose gel electrophoresis. Among the 54 samples analyzed, 27 were Val/Val carriers, 22 were Val/Met carriers, and five were Met/Met carriers. The Val/Met and Met/Met carriers were combined as Met-carriers for subsequent analysis.

Statistical analysis

Chi square test was utilized to examine whether the distribution of the *COMT* genotype deviated from the Hardy-Weinberg equilibrium. Chi square tests, Fisher's exact tests, and *t*-tests were applied to compare differences in demographics, negative symptoms, other clinical symptoms, and IQ between the two genotype groups (*COMT* Met-carriers and Val homozygotes). Where applicable, multiple linear regression analysis was conducted to control for potential confounding variables. Pearson's correlation analyses and *t*-tests were used to identify potential indicators associated with negative symptoms in the total sample, including scores from the four WAIS-RC subtests and the total score, educational level, age, chlorpromazine equivalents, duration of illness, gender, employment and marriage.

Pearson's correlation analyses were used to assess the correlation of negative symptoms with information, similarities in *COMT* Met-carriers and Val homozygotes. Following Fisher's *r* to *z* transformation, *Z*-tests were employed to compare the correlation coefficients between the two genotype groups[35]. Additionally, multiple linear regression analyses were conducted to investigate the interaction effects of information, similarities and the genotype, and other influential factors in relation to negative symptoms. The variables were standardized to reduce collinearity in the multiple linear regression. All the above analyses were conducted in SPSS 20.0 (SPSS Inc., Chicago, IL, United States), and the results were visualized with the ggplot2 package in R version 4.2.3. Statistical significance was established at $P < 0.05$.

RESULTS

Demographics, clinical symptoms, and IQ of the genotype groups

The distribution of the *COMT* genotype showed no deviation from the Hardy-Weinberg equilibrium ($\chi^2 = 0.013$, $P = 0.993$). Met-carriers showed significantly lower scores in negative symptoms than Val homozygotes ($t_{52} = -2.138$, $P = 0.037$) (Table 1) (Figure 1A). The inclusion of employment as a covariate did not significantly alter the results.

Correlations between negative symptoms and IQ, demographics, clinical characteristics in the total sample

In the total sample, significant negative correlations were observed between negative symptoms and information ($r = -0.405$, $P = 0.002$), similarities ($r = -0.475$, $P < 0.001$) (Figure 1B and C). In addition, negative symptoms also correlated with picture completion, block design, WAIS-RC total scores and educational level (all $P < 0.05$) (Table 2). However, *t*-test did not reveal any significant effects of gender, employment, and marital status on negative symptoms (Table 3).

Correlations of negative symptoms with IQ and educational level in the genotype groups

Negative symptoms were associated with information ($r = -0.544$, $P = 0.003$) and similarities ($r = -0.620$, $P = 0.001$) in Val homozygotes only (Figure 1D-G). Moreover, the correlation coefficients of information and similarities with negative symptoms showed significant differences between the two genotype groups (information, $Z = 1.768$, $P = 0.038$;

Table 1 Demographics, clinical symptoms and intelligence quotient in catechol-O-methyltransferase Met-carriers and Val homozygotes

	Met-carriers, *n* = 27		Val homozygotes, *n* = 27		Statistic	*u* value	*P* value
	Mean	SD	Mean	SD			
Age	34.59	7.66	33.15	7.23	$t = 0.713$	52	0.479
Educational level	14.37	3.52	14.98	3.90	$t = -0.604$	52	0.548
Female/male	16/11		14/13		$\chi^2 = 0.300$	1	0.584
Han nationality/non	24/3		25/2		NA	NA	1.000
Employment/non	8/19		15/12		$\chi^2 = 3.711$	1	0.054
Marriage/non	12/15		10/17		$\chi^2 = 0.307$	1	0.580
Current smoker/non	3/24		3/24		NA	NA	1.000
Clozapine user/non	5/22		4/23		NA	NA	1.000
Chlorpromazine equivalents	474.96	258.23	426.50	323.60	$t = 0.608$	52	0.546
Duration of illness	11.73	8.56	11.24	7.51	$t = 0.223$	52	0.825
PANSS positive	9.48	3.89	8.56	2.90	$t = 0.992$	52	0.326
PANSS negative	11.15	3.31	13.59	4.93	$t = -2.138$	52	0.037
PANSS general	21.48	5.15	20.59	3.86	$t = 0.718$	52	0.476
PANSS total	42.11	10.02	42.74	7.89	$t = -0.257$	52	0.799
WAIS-RC information	20.67	4.66	18.41	4.80	$t = 1.756$	52	0.085
WAIS-RC similarities	18.67	2.27	18.33	2.76	$t = 0.485$	52	0.630
WAIS-RC picture completion	11.41	3.12	10.15	2.80	$t = 1.563$	52	0.124
WAIS-RC block design	36.19	7.19	36.44	8.44	$t = -0.122$	52	0.904
WAIS-RC total	106.61	9.75	103.00	10.54	$t = 1.306$	52	0.197

COMT: Catechol-O-methyltransferase; PANSS: Positive and negative syndrome scale; WAIS-RC: Chinese version of the Wechsler adult intelligence scale.

similarities, $Z = 1.726$, $P = 0.042$).

Given the marginally significant effects of chlorpromazine equivalents ($P = 0.076$) and gender ($P = 0.057$) on negative symptoms in the univariate analyses, these variables were subsequently included in the multiple linear regression analyses. In these analyses, negative symptoms were treated as the dependent variable, with *COMT* genotype, information or similarities, the product of *COMT* genotype and information or similarities, gender, and chlorpromazine equivalents serving as independent variables. Multiple linear regression analyses further revealed the interaction effects of information, similarities with the genotype in terms of negative symptoms (information, $\beta = -0.282$, 95%CI: -0.552 to -0.011, $P = 0.042$; similarities, $\beta = -0.250$, 95%CI: -0.495 to -0.004, $P = 0.046$; Table 4). However, the effects of gender and chlorpromazine equivalents on negative symptoms were not found to be significant.

DISCUSSION

This study is the first to examine the regulatory role of the *COMT* Val/Met polymorphism in the relationship between negative symptoms and CR in schizophrenia. The results showed that *COMT* Met-carriers exhibited milder negative symptoms than Val homozygotes. In the total sample, negative symptoms were associated with CR reflected by information and similarities. Furthermore, the correlation of negative symptoms with CR was regulated by the *COMT* genotype.

COMT Met-carriers showed fewer negative symptoms than Val homozygotes. This observation aligns with the findings of Wang *et al*[29], who reported milder negative symptoms in Met-carriers among older patients with schizophrenia. Bosia *et al*[36] documented that the *COMT* genotype influenced the improvement of negative symptoms in patients with schizophrenia after taking clozapine. These findings support the statement that prefrontal dopamine levels mediated by the *COMT* genotype contribute to inter-individual variability of negative symptoms[1].

Negative symptoms were negatively related to CR and IQ. Similarly, Bucci *et al*[37] and Chang *et al*[9] reported that patients with poor CR exhibited more severe primary negative symptoms and worse working memory in cross-sectional studies. Furthermore, prospective studies found CR to be predictive of improvements in the negative symptoms or persistent negative symptoms within 1-10 years after first-episode psychosis[8,11,38]. CR-related factors may mitigate the effect of the disease pathology on the clinical phenotype through fostering new connections between neurons or different

Table 2 Correlations between negative symptoms and intelligence quotient, demographics, clinical characteristics in total participants (*n* = 54)

		Information	Similarities	Picture completion	Block design	WAIS-RC total	Education	Age	CE	Duration of illness
PANSS negative	*r* value	-0.405	-0.475	-0.332	-0.385	-0.527	-0.384	0.019	-0.243	-0.119
	P value	0.002	< 0.001	0.014	0.004	< 0.001	0.004	0.894	0.076	0.391

PANSS: Positive and negative syndrome scale; WAIS-RC: Chinese version of the Wechsler adult intelligence scale; CE: Chlorpromazine equivalents.

Table 3 The effects of gender, employment and marriage on negative symptoms

	Gender/employment/marriage	*n*	Mean	SD	*t* value	*u* value	*P* value
PANSS negative	Male	24	13.63	4.79	1.949	52	0.057
	Female	30	11.37	3.73			
	Employed	23	11.91	3.85	-0.663	52	0.510
	Non	31	12.71	4.71			
	Married	32	12.09	4.71	-0.561	52	0.577
	Non	22	12.77	3.80			

PANSS: Positive and negative syndrome scale.

Table 4 Correlations of negative symptoms with information, similarities in catechol-O-methyltransferase met-carriers and Val homozygotes

			Information	Similarities
PANSS negative	Met-carriers (*n* = 27)	*r* value	-0.099	-0.223
		P value	0.624	0.263
	Val/Val (*n* = 27)	*r* value	-0.544	-0.62
		P value	0.003	0.001
	Correlation coefficient comparison	*Z* value	1.768	1.726
		P value	0.038	0.042
	Interaction test[1]	*β* value	-0.282	-0.250
		95%CI	-0.552 to -0.011	-0.495 to -0.004
		P value	0.042	0.046

[1]In the multiple linear regression, negative symptoms were treated as the dependent variable, with catechol-O-methyltransferase (*COMT*) genotype, information or similarities, the product of *COMT* genotype and information or similarities, gender, and chlorpromazine equivalents serving as independent variables.
PANSS: Positive and negative syndrome scale.

brain regions, activating compensatory neural networks, or enhancing the efficiency of existing neural network connections[39,40]. Nevertheless, the detailed mechanisms are yet to be elucidated, and relevant research remains limited in schizophrenia.

Our study did not observe significant effects of demographic or clinical characteristics on negative symptoms. However, previous research has identified several factors associated with negative symptoms, such as gender[41], psychiatric comorbidities, medication side effects, and prenatal events[42]. This discrepancy arises because our study did not collect data on some of these factors, and its ability to detect factors weakly correlated with negative symptoms was constrained due to the small sample size. Additionally, antipsychotics may impair the ability to attribute incentive salience and drive by blocking dopamine receptors, thus leading to secondary negative symptoms or exacerbating primary negative symptoms[43]. However, our study did not find an association between antipsychotic dose and negative symptoms,

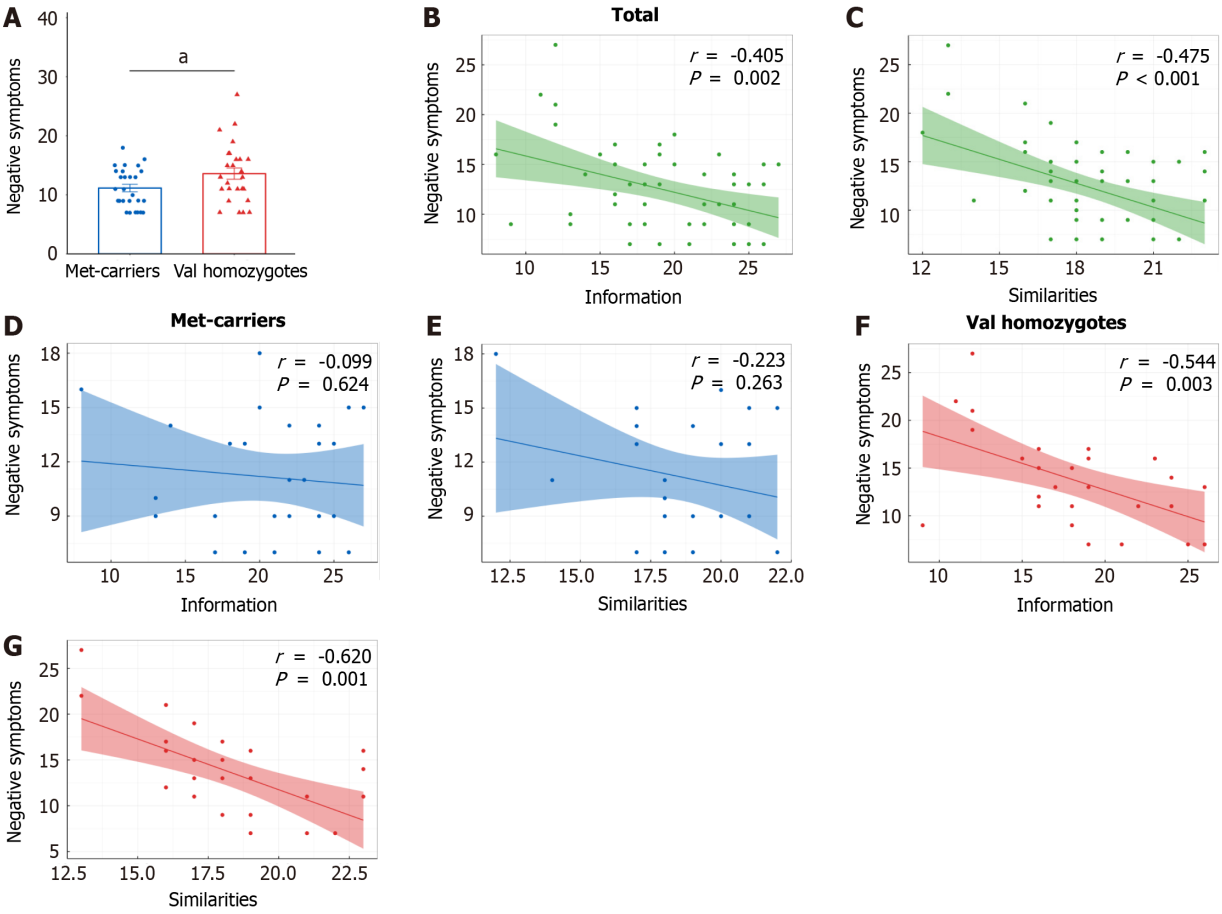

Figure 1 Catechol-O-methyltransferase genotypes, negative symptoms, information and similarities. A: Comparison of negative symptoms across catechol-O-methyltransferase genotypes; B: Association between information and negative symptoms in the entire sample; C: Association between similarities and negative symptoms in the entire sample; D: Correlation of information with negative symptoms in Met-carriers; E: Correlation of similarities with negative symptoms in Met-carriers; F: Association between information and negative symptoms in Val homozygotes; G: Association between similarities and negative symptoms in Val homozygotes. $^{a}P < 0.05$.

consistent with the results of a clinical trial involving 520 patients with schizophrenia[43]. These findings suggest that the negative impact of antipsychotics on negative symptoms may be mild.

The relationship of negative symptoms with CR was regulated by the *COMT* genotype. This study is a novel report in the context of schizophrenia. Similarly, research demonstrated that CR interacted with the apolipoprotein ε4 (*APOE*-ε4) genotype, a genetic risk factor for dementia, in relation to cognitive function in healthy elders[44]. CR may have a stronger protective effect against the risk of dementia in APOE-ε4 carriers[45]. These findings may suggest that in increased pathological states, there is greater room for clinical phenotype improvement, thereby leading to more pronounced protective effects of CR.

Considering that the protective effect of CR is evident only in the early stages of dementia[46,47], further investigation is warranted to determine whether a similar threshold phenomenon exists in the interaction effects of certain factors with CR in terms of the clinical phenotype of schizophrenia. Nonetheless, the current findings hold implications for the individualized and comprehensive intervention of negative symptoms in clinically stable patients with schizophrenia, suggesting that the intervention for negative symptoms in *COMT* Val homozygotes may require the application of more CR strategies. Additionally, our findings indicate that the effect of *COMT* on negative symptoms may be influenced by complex factors. This complexity might result in negative outcomes in clinical trials of *COMT* inhibitors for negative symptoms[48], despite the effect of *COMT* genotype on dopamine activity suggesting the potential efficacy of *COMT* inhibitors[49].

One of the strengths of this study is that it is the first report on the regulatory effect of the *COMT* genotype on the relationship between CR and negative symptoms. Additionally, all participants were clinically stable patients, thereby reducing potential confounding effects of fluctuating medications and clinical symptoms on the findings. Despite this, this study has some limitations that need to be acknowledged. Firstly, as a cross-sectional survey, it could not establish the dynamic and causal relationships among CR, *COMT* genotype and negative symptoms, necessitating further cohort studies and intervention trials. Secondly, the relatively small sample size limited the generalizability of the findings, thus requiring validation through larger-scale studies. Thirdly, due to the limited sample size, we combined the Val/Met and Met/Met carriers into a single group identified as Met-carriers. Although this grouping strategy is a common analysis approach[50-52], it may overlook valuable information that warrants further investigation in studies with larger sample sizes. Fourthly, this study did not comprehensively collect potential factors influencing negative symptoms and faced

limitations in detecting weakly associated factors due to the small sample size. Lastly, due to relatively mild negative symptoms of the participants, it remains unknown whether the interaction effects of CR and the *COMT* genotype are influenced by negative symptom severity.

CONCLUSION

In summary, our study showed that the correlation between negative symptoms and CR was regulated by the *COMT* Val/Met polymorphism. The findings enhance the understanding of the mechanisms underlying individual differences in negative symptoms and provide insightful evidence for the individualized and comprehensive intervention of negative symptoms in schizophrenia.

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FOOTNOTES

Author contributions: Wang CY was the guarantor and designed the study; Hou WP, Qin XQ, Hou WW, Zhou FC, and Dong F participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Han YY, Bo QJ, Li XB, and Wang CY revised the manuscript.

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ORIGINAL ARTICLE

Observational Study

Mental health and insomnia problems in healthcare workers after the COVID-19 pandemic: A multicenter cross-sectional study

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Abstract

BACKGROUND

Healthcare workers (HCWs) are at increased risk of contracting coronavirus disease 2019 (COVID-19) as well as worsening mental health problems and insomnia. These problems can persist for a long period, even after the pandemic.

However, less is known about this topic.

AIM

To analyze mental health, insomnia problems, and their influencing factors in HCWs after the COVID-19 pandemic.

METHODS

This multicenter cross-sectional, hospital-based study was conducted from June 1, 2023 to June 30, 2023, which was a half-year after the end of the COVID-19 emergency. Region-stratified population-based cluster sampling was applied at the provincial level for Chinese HCWs. Symptoms such as anxiety, depression, and insomnia were evaluated by the Generalized Anxiety Disorder-7, Patient Health Questionnaire-9, and Insomnia Severity Index. Factors influencing the symptoms were identified by multivariable logistic regression.

RESULTS

A total of 2000 participants were invited, for a response rate of 70.6%. A total of 1412 HCWs [618 (43.8%) doctors, 583 (41.3%) nurses and 211 (14.9%) nonfrontline], 254 (18.0%), 231 (16.4%), and 289 (20.5%) had symptoms of anxiety, depression, and insomnia, respectively; severe symptoms were found in 58 (4.1%), 49 (3.5%), and 111 (7.9%) of the participants. Nurses, female sex, and hospitalization for COVID-19 were risk factors for anxiety, depression, and insomnia symptoms; moreover, death from family or friends was a risk factor for insomnia symptoms. During the COVID-19 outbreak, most [1086 (76.9%)] of the participating HCWs received psychological interventions, while nearly all [994 (70.4%)] of them had received public psychological education. Only 102 (7.2%) of the HCWs received individual counseling from COVID-19.

CONCLUSION

Although the mental health and sleep problems of HCWs were relieved after the COVID-19 pandemic, they still faced challenges and greater risks than did the general population. Identifying risk factors would help in providing targeted interventions. In addition, although a major proportion of HCWs have received public psychological education, individual interventions are still insufficient.

Key Words: COVID-19; Mental health; Psychological symptoms; Insomnia; Sleep disorders; Cross-sectional study; Epidemiological study

Core Tip: Limited information is known about mental health and insomnia problems among healthcare workers after the coronavirus disease 2019 (COVID-19) pandemic. This multicenter cross-sectional study revealed that 16.4%-20.5% (289) of healthcare workers overall had anxiety, depression, or insomnia symptoms; identified that those who were nurses, were female, had been hospitalized for COVID-19, or died in families or friends were at high risk of symptoms. Although a major proportion of healthcare workers have received public psychological education, individual interventions are still not sufficient.

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INTRODUCTION

Since the end of December 2019, the infectious disease coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1], has rapidly spread and become a worldwide sudden pandemic threatening global health and leading to societal instability[2]. Apart from various respiratory and associated symptoms of COVID-19[3], population mental health problems are also of increasing global concern[4]. During the COVID-19 epidemic, the worries and uncertainty of infections, physical distancing and decreased outside activities caused by associated lockdowns[5,6] could negatively affect mental health and cause psychological symptoms such as anxiety, depression, insomnia, and others[6,7]. Healthcare workers (HCWs), who play key roles in the prevention, diagnosis, treatment, and care of patients and the public, are at increased risk of contracting COVID-19 and developing psychological distress, sleep problems, and other mental health symptoms[8-11]. Previous studies revealed that nearly half of HCWs reported experiencing psychological symptoms during the COVID-19 pandemic[9,12].

China is one of the countries most strongly affected by COVID-19[3]. After approximately three years of control of the disease and the advance of COVID-19 vaccines[13], the Chinese government announced the end of the COVID-19 emergency and eased pandemic control in December 2022[14]. However, the impact of psychological symptoms can even last for a long period, even after the pandemic[15]. Previous experience with severe acute respiratory syndrome (SARS) survivors revealed that the psychological implications of infectious diseases could include chronic effects[16,17]. For HCWs, the increased risk and severity of psychological symptoms and sleep disturbances could persist for a long time, which could not only be harmful to their mental health[18] but also influence their clinical practice[8]. However, limited studies have been conducted in this field, which is a research gap. Thus, we conducted this multicenter cross-sectional study of mental health problems, insomnia problems, and their influencing factors in HCWs after the COVID-19 pandemic. This study can be helpful for exploring the prevalence of these problems in the post-COVID-19 era and identifying potential HCWs at increased risk for targeted interventions to promote universal mental health.

MATERIALS AND METHODS

Study design and sampling process

This study was conducted following the STROBE statement[19] and was reviewed and approved by the local ethics committee (No. 2023226). Informed consent was provided by all participants prior to enrollment by clicking the "agree to the consent" button online on the guiding page of the electronic questionnaire. This study followed the Declaration of Helsinki, and all the surveys were anonymous and provided assurance of confidentiality.

This was a multicenter cross-sectional, hospital-based study from June 1, 2023 to June 30, 2023; this was a half-year after the Chinese government announced the end of the COVID-19 emergency and eased pandemic control (December 2022)[14]. The aim of this study was to evaluate mental health and insomnia problems in HCWs after the COVID-19 pandemic and to identify the potential influencing factors. The sampling was conducted in Shandong Province, which is located in eastern China and has 101.6 million residents and 1.8 million local HCWs in 2022[20]; this region serves as a sufficient representative area with nearly one-fourteenth of the Chinese population. Generally, we applied region-stratified population-based cluster sampling based on our profound previous experience[6,21,22] as follows: (1) First, the sampling site was geographically stratified as western, middle, or eastern regions[21] with one coordinating center in each region; (2) second, the research team determined the required number of participants with different characteristics (populations of regions, healthcare positions, technical titles, places of residence, and hospital levels) based on proportions of local groups for representativeness; (3) third, one frontline (*e.g.*, doctors and nurses) department and one nonfrontline (*e.g.*, pharmacist and laboratorian) department were randomly sampled from each selected hospital, and all of their affiliated HCWs were asked to participate in this study; and (4) finally, the HCWs from 29 hospitals (level III n = 4, level II n = 5, 1 level I n = 7, and community n = 13; classified according to the National Health Commission) were enrolled and summarized in a unified anonymous database for analysis.

Study population and eligibility criteria

The target sample size was calculated with PASS software (NCSS LLC., Kaysville, Utah; version 21) to determine the odds ratio (OR) *via* logistic regression. The statistical power was set at 90%, and the alpha coefficient was 0.05 according to the two-sided Wald test[23]. At least 1211 valid questionnaires were needed. After eliminating a potential 30% dropout rate, the dropout-inflated expected invited number of participating HCWs should be no less than 1730. Considering the regional allocation proportions, a total of 2000 surveys were sent (western, n = 650; central, n = 700; and eastern, n = 650).

The inclusion criteria for HCWs were as follows: (1) Resided and served as HCWs in Shandong Province during and after the COVID-19 pandemic; (2) were defined as workers who had direct or indirect exposure to patients and were involved in patient care; (3) were aged no less than 18 years; and (4) provided informed consent. Questionnaires with: (1) Abnormal response times (< 1 min or > 1 h); (2) no trust questions; or (3) incomplete responses were regarded as invalid surveys.

Questionnaire and assessments

The questionnaire included 4 parts. The first part was a guiding page to introduce the purpose, design, and informed consent of this study. In the second part, the questionnaire collected technical profiles, demographic characteristics, and experience related to COVID-19. The technical profile consisted of healthcare position, technical title, place of residence (urban or rural), hospital served (classified into level III, level II, level I, or community), demographic characteristics (classified into western, middle, or eastern), sex, age (classified into 18-34, 35-49, or ≥ 50 years to consist of studies on Chinese mental health during the normal[24] and COVID-19 periods[6,21,22] for comparison), education level, marital status, and experience related to COVID-19-related clinical practices during the COVID-19 pandemic, experiences of COVID-19, experiences of families/friends during the COVID-19 pandemic, and psychological intervention during the COVID-19 pandemic. The third part included standard mental health measurement tools [the Generalized Anxiety Disorder-7 scale (GAD-7) for evaluating anxiety symptoms and the Patient Health Questionnaire-9 (PHQ-9) for evaluating depression symptoms] and insomnia problems [the Insomnia Severity Index (ISI) for assessing insomnia symptoms]. Participants were required to answer questions mainly about their feelings about the past 2 wk. The final part consisted of 2 trust questions, "I answered truthfully (yes or no)" and "What is ten plus ten?".

All the assessment tools used were validated Chinese versions of self-reported screening scales, with Cronbach's α values of 0.93, 0.86, and 0.85 for the GAD-7[25], PHQ-9[26], and ISI[27], respectively. A higher score on these scales indicated a greater likelihood of having more severe symptoms (maximum scores of 21, 27, and 28 on the GAD-7, PHQ-9,

and ISI, respectively). A GAD-7 score, PHQ-9 score, and ISI ≥ 10, ≥ 10, and ≥ 15 indicate symptoms of anxiety, depression, and insomnia, respectively, while scores ≥ 15, ≥ 15, and ≥ 22 indicate severe symptoms. These cutoff scores for detecting symptoms were determined according to Chinese norms and the consensus of neuropsychologists and are widely recognized in psychological studies of the Chinese population[6,10,21,22,28].

Statistical analysis

The Kolmogorov-Smirnov test was used to explore the distributions of continuous data. After all the tested variables were normally distributed, correlation analysis was performed to explore the relationships among the scores of the different scales by Pearson's correlation. To explore the potential influencing factors (technical profiles, demographic characteristics, and experiences related to COVID-19) of anxiety, depression and insomnia symptoms, multivariable logistic regression was conducted. Variables with a *P* value less than 0.10 in the univariate logistic regression were subsequently entered into a multivariate logistic analysis for adjustment (in a backward fashion), and ORs with 95%CI: are presented. All significance levels were set at $\alpha = 0.05$, and all tests were 2-tailed. All the statistical analyses were performed using SPSS statistics software (IBM, Armonk, NY, United States; version 27).

RESULTS

Demographic characteristics of the participants

Generally, 2000 participants were invited to complete 1503 surveys. After excluding 91 invalid questionnaires (abnormal response time, $n = 32$; failure to answer any trust questions, $n = 19$; and incomplete questions, $n = 40$), a total of 1412 HCWs were ultimately enrolled. The final included questionnaires met the minimum sample size requirement, which was calculated previously. The overall response rate was 70.6%.

The technical profiles, demographic characteristics, and experiences related to COVID-19 of all included participants are shown in Table 1. A total of 1412 HCWs [618 (43.8%) doctors, 583 (41.3%) nurses, and 211 (14.9%) nonfrontline], 855 (60.6%), 432 (30.6%), and 125 (8.9%) participants had junior, intermediate, and senior technical titles, respectively. The majority of them (1319 (93.4%)] were residents of urban areas. A total of 829 (58.7%), 423 (30.0%), 109 (7.7%), and 51 (3.6%) HCWs served in level III, level II, level I, and community hospitals, respectively. Regarding demographic characteristics, 441 (31.2%), 502 (35.6%), and 469 (33.2%) of the participants worked in the western, middle, and eastern regions of Shandong, respectively. Most participants were women [803 (56.9%)], aged 18 to 34 years [691 (48.9%)], had an educational level of undergraduate or lower [980 (69.4%)], and were married [955 (67.6%)]. The technical and demographic data of the included participants were comparable to those of the local HCW population[20], suggesting sufficient representativeness.

With regard to COVID-19-related experiences, 574 (40.7%) and 445 (31.5%) HCWs provided isolated care for COVID-19 patients and hospitalized care for infections during the COVID-19 epidemic, respectively. Among the HCWs, the majority [1145 (81.1%)] were infected with COVID-19 without hospitalization, while 17.9% (253) of them experienced hospitalization related to COVID-19. In addition, 601 (42.6%) and 387 (27.4%) HCWs were hospitalized and died, respectively, from their families or friends related to COVID-19. During the COVID-19 outbreak, most [1086 (76.9%)] of the participating HCWs received psychological interventions, while nearly all [994 (70.4%)] of them had received public psychological education. Only 7.2% (102) of the HCWs received individual counseling from COVID-19.

Mental health, insomnia problems, and correlations

Table 2 shows the mental health, insomnia problems, and correlations of all the included HCWs. Among those assessed by the GAD-7, PHQ-9, and ISI, 18.0% (254), 16.4% (231), and 20.5% (289) of the included HCWs had symptoms of anxiety, depression, and insomnia, respectively. Severe anxiety, depression, and insomnia symptoms were found in 4.1% (58), 3.5% (49), and 7.9% (111) of the participants, respectively.

Analysis of the potential correlations among the scores on these scales revealed that the GAD-7 and ISI scores ($r = 0.494$, $P < 0.001$) as well as the PHQ-9 and ISI scores ($r = 0.684$, $P < 0.001$) were both significantly positively correlated. However, the correlation between the GAD-7 score and the PHQ-9 score did not reach statistical significance ($r = 0.494$, $P = 0.09$).

Influential factors and high-risk populations

To identify the factors influencing mental health and insomnia problems and explore potential populations at high risk of symptoms, multivariable logistic regressions were conducted.

For anxiety symptoms, healthcare position, sex, clinical practice during the COVID-19 pandemic, and experience with family or friends were entered into the multivariable analysis. After multivariable adjustment, age (OR = 1.114, 95%CI: 1.054-1.178, $P = 0.001$), female sex (OR = 1.052, 95%CI: 1.003-1.105, $P = 0.04$), and hospitalization for COVID-19 infection (OR = 2.047, 95%CI: 1.003-1.105, $P = 0.04$) were found to be independent risk factors for anxiety symptoms (Table 3).

The symptoms of depression, healthcare position, sex, clinical practice during the COVID-19 pandemic, and experience with family or friends were entered into the multivariable analysis. After multivariable adjustment, age (OR = 1.092, 95%CI: 1.029-1.160, $P = 0.014$), female sex (OR = 1.148, 95%CI: 1.085-1.214, $P < 0.001$), and hospitalization for COVID-19 infection (OR = 1.662, 95%CI: 1.476-1.855, $P < 0.001$) were found to be independent risk factors for depression symptoms (Table 4).

Table 1 Technical profiles, demographic characteristics, and experiences related to COVID-19 of all included healthcare workers (*n* = 1412)

Variable	*n*	%
Technical profile		
Healthcare position		
Doctors	618	43.8
Nurses	583	41.3
Nonfrontline[1]	211	14.9
Technical title		
Junior	855	60.6
Intermediate	432	30.6
Senior	125	8.9
Place of residence		
Urban	1319	93.4
Rural	93	6.6
Served hospital level		
Level III	829	58.7
Level II	423	30.0
Level I	109	7.7
Community	51	3.6
Demographic characteristics		
Region		
Western	441	31.2
Middle	502	35.6
Eastern	469	33.2
Sex		
Male	609	43.1
Female	803	56.9
Age, yr		
18-34	691	48.9
35-49	443	31.4
≥ 50	278	19.7
Education level		
≤ Undergraduate	980	69.4
≥ Postgraduate	432	30.6
Marriage status		
Unmarried	425	30.1
Married	955	67.6
Divorced/widowed	32	2.3
Experience related to COVID-19		
Clinical practice during COVID-19		
Isolated care of COVID-19 contacts	574	40.7
Hospitalized care of infections	445	31.5

None	393	27.8
Experience of COVID-19		
Infected without hospitalization	1145	81.1
Hospitalization related to COVID-19	253	17.9
Did not infected	14	1.0
Experience of families/friends		
Hospitalization related to COVID-19	601	42.6
Death related to COVID-19	387	27.4
None	424	3
Psychological intervention from COVID-19		
Yes	1086	76.9
Public psychological education	994	70.4
Individual counseling	102	7.2
None	326	23.1

[1]Pharmacist, laboratorian, and other healthcare workers who indirectly exposed patients but also served in healthcare settings.
HCWs: Healthcare workers; COVID-19: Coronavirus disease 2019.

Table 2 Mental health, insomnia problems, and their correlations of all included healthcare workers (*n* = 1412)

Mental health and insomnia problems	*n*	%
Scale/symptom		
GAD-7		
Anxiety symptoms	254	18.0
Severe anxiety symptoms	58	4.1
PHQ-9		
Depression symptoms	231	16.4
Severe depression symptoms	49	3.5
ISI		
Insomnia symptoms	289	20.5
Severe insomnia symptoms	111	7.9
Correlation	*r*	*P*
GAD-7 with PHQ-9	0.494	0.09
GAD-7 with ISI	0.719	< 0.001[a]
PHQ-9 with ISI	0.684	< 0.001[a]

[a]$P < 0.01$.
HCWs: Healthcare workers; GAD-7: Generalized Anxiety Disorder-7 Scale; PHQ-9: Patient Health Questionnaire-9; ISI: Insomnia Severity Index.

The presence of insomnia problems was also analyzed, and healthcare position, sex, clinical practice during the COVID-19 pandemic, and experience with family or friends were significantly different ($P < 0.10$) according to univariate analysis. After multivariable adjustment, nurse sex (OR = 1.126, 95%CI: 1.057-1.199, $P < 0.001$), female sex (OR = 1.074, 95%CI: 1.019-1.131, $P = 0.009$), hospitalization for COVID-19 infection (OR = 1.085, 95%CI: 1.016-1.159, $P = 0.01$), and experience of death in families or friends (OR = 2.082, 95%CI: 1.765-2.510, $P < 0.001$) were found to be independent risk factors for insomnia symptoms (Table 5).

Table 3 Factors associated with anxiety symptoms (Generalized Anxiety Disorder-7 Scale) of all included healthcare workers (*n* = 1412) by multivariate logistic regression

Variable	OR	95%CI	*P* value
Healthcare position			
Doctors	Contract	-	-
Nurses	1.114	1.054-1.178	0.001[b]
Nonfrontline	0.978	0.919-1.039	0.57
Sex			
Male	Contract	-	-
Female	1.052	1.003-1.105	0.04[a]
Clinical practice during COVID-19			
Isolated care of COVID-19 contacts	Contract	-	-
Hospitalized care of infections	2.047	1.675-2.236	< 0.001[b]
None	0.941	0.872-1.016	0.14
Experience of families/friends			
Hospitalization related to COVID-19	Contract	-	-
Death related to COVID-19	1.048	0.982-1.120	0.17
None	0.870	0.817-1.126	0.32

[a]$P < 0.05$.
[b]$P < 0.01$.
HCWs: Healthcare workers; GAD-7: Generalized Anxiety Disorder-7 Scale; COVID-19: Coronavirus disease 2019; OR: Odds ratio.

DISCUSSION

Epidemiological studies are important resources and evidence for guiding healthcare practice, decision making, and disease prevention, thus benefiting public health[29,30]. This large-scale multicenter cross-sectional study involving 1412 samples from a representative cohort of HCWs revealed that 18.0%, 16.4%, and 20.5% of HCWs had symptoms of anxiety, depression, and insomnia, respectively, and severe symptoms were found in 4.1%, 3.5%, and 7.9% of participants, respectively. Several studies concerning mental health and sleep problems in HCWs during the COVID-19 pandemic have been performed. Lai *et al*[9] performed a cross-sectional study in early 2020 with Chinese HCWs and revealed a considerable proportion of symptoms of depression (50.4%), anxiety (44.6%), and insomnia (34.0%)[9]. Evidence from meta-analyses has also shown that high proportions of global HCWs have psychological and sleep problems[10-12]. Two meta-analyses by Saragih *et al*[12] and Pappa *et al*[10] conducted reported prevalences of anxiety, depression, and insomnia symptoms in HCWs of 23%-40%, 22%-37%, and 38%, respectively, while another meta-analysis by Aymerich *et al*[11] performed in 2022 suggested that 42%, 33%, and 42%, respectively, of HCWs exposed to COVID-19 reported depressive symptoms, anxiety features, and insomnia. Compared with these studies concerning HCWs during the COVID-19 pandemic, the results of the present study performed half a year after the pandemic suggested overall improvements in mental health and sleep problems.

However, it should be noted that, compared with HCs in the general population during the normal period and during the COVID-19 pandemic, HCWs in the post-COVID-19 era still have a greater risk of severe psychological and sleep symptoms. According to an epidemiological study by Huang *et al*[24] before the COVID-19 pandemic (during the normal period), the lifetime prevalence of anxiety and depression in the general Chinese population should be 6.8% and 7.6%, respectively[24]. Our team also performed several cross-sectional studies during different periods of the COVID-19 pandemic and revealed that overall, 11.0%-21.7% of the general Chinese population had anxiety, depression, or insomnia symptoms, and 1.9%-5.6% had severe symptoms[6,21,22]. The prevalence of depression, anxiety, and insomnia was also reported to be 15.97%, 15.15%, and 23.87%, respectively, for the global general population in previous studies[31]. After the COVID-19 pandemic, the general population reported decreased risks and levels of mental health problems, and their long-term prevalence gradually became comparable to that during normal periods; additionally, they typically experienced no or mild symptoms[15]. However, this study revealed a considerable prevalence of psychological and sleep symptoms in HCWs after COVID-19. Importantly, experience from the 2003 SARS epidemic suggested that the psychological impact of HCWs can be sustained for at least 1 year[18], suggesting that additional attention needs to be given to the long-term mental and sleep health of HCWs, even in the post-COVID-19 era. Together, our findings suggest that although the mental health and sleep problems of HCWs were relieved after the COVID-19 pandemic, they still faced challenges and greater risks than did the general population.

Table 4 Factors associated with depression symptoms (Patient Health Questionnaire-9) of all included healthcare workers (*n* = 1412) by multivariate logistic regression

Variable	OR	95%CI	*P* value
Healthcare position			
Doctors	Contract	-	-
Nurses	1.092	1.029-1.160	0.014[a]
Nonfrontline	0.958	0.898-1.021	0.244
Gender			
Male	Contract	-	-
Female	1.148	1.085-1.214	< 0.001[b]
Clinical practice during COVID-19			
Isolated care of COVID-19 contacts	Contract	-	-
Hospitalized care of infections	1.662	1.476-1.855	< 0.001[b]
None	0.924	0.752-1.136	0.48
Experience of families/friends			
Hospitalization related to COVID-19	Contract	-	-
Death related to COVID-19	1.077	0.991-1.170	0.09
None	0.970	0.893-1.052	0.48

[a]$P < 0.05$.
[b]$P < 0.01$.
HCWs: Healthcare workers; PHQ-9: Patient Health Questionnaire-9; COVID-19: Coronavirus disease 2019; OR: Odds ratio.

Another major finding is the identification of factors influencing psychological and sleep symptoms, thus providing guidance for targeted interventions for high-risk HCWs. In general, being a nurse or female and being hospitalized for COVID-19 infection were risk factors for anxiety, depression, and insomnia. Moreover, the experience of death from family or friends was a risk factor for insomnia symptoms. Nurses were also found to be at high risk of having psychological symptoms during the COVID-19 pandemic[9,10]. Frontline nurses were likely to be at the highest risk of infection and became witnesses of COVID-19 patients and deaths[10,32]. Additionally, they might even work longer hours than usual and undertake more night shifts and overtime during the COVID-19 pandemic[8]. All these factors might lead to a high risk of psychological and sleep problems for nurses even after COVID-19. Previous studies also reported higher rates and levels of affective symptoms in female HCWs than in male HCWs[9,10]. In addition, studies of the general population during the COVID-19 pandemic also suggested that females were affected more by the pandemic than males were[33,34]. In summary, particular attention is warranted regarding mental health and sleep problems for nurses and women. The clinical practice and experience of families or friends during the COVID-19 pandemic were also related to mental health and sleep problems. These traumatic experiences, such as witnessing deaths and suffering patients, might cause long-term psychological symptoms and even lead to posttraumatic stress disorder (PTSD)[35]. It will be critical to provide effective targeted psychological interventions for HCWs with COVID-19 even after its onset to reduce their risk of mental health and sleep problems and to enhance their resilience after the pandemic.

Finally, this study revealed that most (76.9%) of the participating HCWs received psychological intervention during the COVID-19 outbreak. This proportion is significantly greater than that in the general population (16.2%-17.4%)[6,21,22]. This finding provides encouraging evidence that a major proportion of HCWs have received timely psychological interventions. However, as 3.5%-7.9% of HCWs reported severe psychological and sleep problems after the COVID-19 pandemic, additional efforts are still needed to provide further interventions in the post-COVID-19 era. Crucially, only 7.2% of the HCWs had individual counseling, while the others only received public psychological education. For HCWs with severe symptoms, individualized systemic psychological interventions with standard phases are preferred[29], but the current supply is insufficient. This epidemiological study of the factors influencing psychological symptoms would be helpful for identifying groups at high risk and providing targeted interventions.

It should be noted that this study has several limitations. First, to reduce the duration of the survey and due to limitations in the study design, this study did not cover symptoms of PTSD, which could be a future research direction. Second, although we applied province-level cluster sampling, additional efforts are still needed to develop a nationwide random sampling study for improved representativeness. Third, although a tolerable response rate (70.6%) and sample size (n = 1412) were needed in this study, response bias may still exist. Finally, the study was carried out half a year after the COVID-19 pandemic, and further exploration is needed in the future; longitudinal follow-up could provide additional findings.

Table 5 Factors associated with insomnia symptoms (Insomnia Severity Index) of all included healthcare workers (*n* = 1412) by multivariate logistic regression

Variable	OR	95%CI	*P* value
Healthcare position			
Doctors	Contract	-	-
Nurses	1.126	1.057-1.199	< 0.001[b]
Nonfrontline	0.936	0.876-1.001	0.07
Sex			
Male	Contract	-	-
Female	1.074	1.019-1.131	0.009[b]
Clinical practice during COVID-19			
Isolated care of COVID-19 contacts	Contract	-	-
Hospitalized care of infections	1.085	1.016-1.159	0.01[a]
None	0.971	0.743-1.271	0.83
Experience of families/friends			
Hospitalization related to COVID-19	Contract	-	-
Death related to COVID-19	2.082	1.765-2.510	< 0.001[b]
None	0.986	0.904-1.029	0.19

[a]*P* < 0.05.
[b]*P* < 0.01.
HCWs: Healthcare workers; ISI: Insomnia Severity Index; COVID-19: Coronavirus disease 2019; OR: Odds ratio.

CONCLUSION

The results of this survey on mental health and insomnia problems in HCWs after the COVID-19 pandemic revealed that 18.0%, 16.4%, and 20.5% of the HCWs experienced symptoms of anxiety, depression, and insomnia, respectively; additionally, severe symptoms were found in 4.1%, 3.5%, and 7.9% of the participants, respectively. Although the mental health and sleep problems of HCWs were relieved after the COVID-19 pandemic, they still faced challenges and greater risks than did the general population. Nurses, female sex, and hospitalization for COVID-19 were risk factors for anxiety, depression, and insomnia symptoms; moreover, death from family or friends was a risk factor for insomnia symptoms. Identification of these risk factors would help in providing targeted interventions. In addition, although a major proportion of HCWs have received public psychological education, individual interventions are still insufficient.

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FOOTNOTES

Author contributions: Ding W collected the data, analyzed the data, and revised the manuscript; Wang MZ designed the study, collected the data, analyzed the data, and revised the manuscript; Zeng XW, Liu ZH, Meng Y, Hu HT, Zhang Y, Guan YG, Meng FG, and Zhang JG collected the data, analyzed the data, and revised the manuscript; Wang S designed the study, collected and analyzed the data, drafted the manuscript, and revised the manuscript; All the authors read and approved the final manuscript. Wang S and Wang MZ contributed equally to this work as co–corresponding authors. Both Wang S and Wang MZ have played important and indispensable roles in the study design, data collection, data interpretation, and manuscript preparation as the co-corresponding authors. Wang S conceptualized, designed, and analzed data for this study. He searched the literature, revised and finished the early version of the manuscript with the focus on mental health and insomnia problems in healthcare workers. Wang MZ was instrumental and responsible for data re-analysis and re-interpretation, comprehensive literature search, preparation and submission of the current version of the manuscript with a new focus on analyzing influencing factors of mental health and insomnia problems. He also supervised the whole process of the project. This collaboration between Wang S and Wang MZ is crucial for the publication of this manuscript and other manuscripts still in preparation.

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ORIGINAL ARTICLE

Observational Study

Prevalence and risk factors of depression among patients with perianal fistulizing Crohn's disease

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Abstract

BACKGROUND

Psychological distress, especially depression, associated with perianal fistulizing Crohn's disease (PFCD) is widespread and refractory. However, there is a surprising paucity of studies to date that have sought to identify the prevalence and risk factors of depression associated with PFCD.

AIM

To estimate the prevalence of depressive symptoms and investigate the depression-related risk factors in patients with PFCD.

METHODS

The study was conducted in the form of survey and clinical data collection *via* questionnaire and specialized medical staff. Depressive symptoms, life quality, and fatigue severity of patients with PFCD were assessed by Patient Health Questionnaire-9, Inflammatory Bowel Disease Patient Quality of Life Questionnaire (IBDQ), and Inflammatory Bowel Disease (IBD) Fatigue Patient Self-

assessment Scale. The basic demographic information, overall disease features, perianal clinical information, and laboratory inflammation indicators were also gathered. Multivariate regression analysis was ultimately used to ascertain the risk factors of depression associated with PFCD.

RESULTS

A total of 123 patients with PFCD were involved, and 56.91% were suffering from depression. According to multivariate logistic regression analysis, Perianal Disease Activity Index (PDAI) score [odds ratio (OR) = 0.69, 95% confidence interval (CI): 0.50 to 0.95], IBDQ score (OR = 0.93, 95%CI: 0.88 to 0.97), modified Van Assche index (OR = 1.24, 95%CI: 1.01 to 1.53), and IBD Fatigue score (OR = 1.72, 95%CI: 1.23 to 2.42) were independent risk factors of depression-related prevalence among patients with PFCD ($P < 0.05$). Multiple linear regression analysis revealed that the increasing perianal modified Van Assche index (β value = 0.166, 95%CI: 0.02 to 0.31) and decreasing IBDQ score (β value = -0.116, 95%CI: -0.14 to -0.09) were independently associated with the severity of depression ($P < 0.05$).

CONCLUSION

Depressive symptoms in PFCD patients have significantly high prevalence. PDAI score, modified Van Assche index, quality of life, and fatigue severity were the main independent risk factors.

Key Words: Crohn's disease; Fistula; Depression; Inflammatory bowel diseases; Risk factors

Core Tip: Perianal fistulizing Crohn's disease (PFCD) is the most prominent, invasive and common lesion among the phenotypes of Crohn's disease (CD). Due to the unique disease experience of PFCD patients, they suffer from severe clinical and psychological consequences like depression. However, there is a lack of studies focusing on the risk factors of depression within specific disease types of CD. In this study, we analyzed the prevalence and risk factors of PFCD with depression, which could assist professionals in early identification and medical intervention in patients with PFCD.

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INTRODUCTION

Crohn's disease (CD), one of the main inflammatory bowel disease (IBD) types, is characterized by chronic nonspecific intestinal inflammation. The clinical features of CD, such as severe symptoms, complex complications, and chronic recurrent state without spontaneous healing, are significant enormous challenges to the physical and mental health of CD patients, who are more likely to be psychologically impaired. As reported by the newest systematic review, the composite morbidity of depressive symptoms in CD patients was around 25.3%[1], which is two to four times greater than the general population, with an approximate incidence rate of 6%[2].

China and other parts of Asia display a higher prevalence of perianal CD, which is one of the most challenging phenotypes of CD. More than half of the adult CD patients are accompanied with perianal lesions[3]. Of those, perianal fistulizing CD (PFCD) is the most prominent, invasive, and common lesion, with a prevalence of about 17% to 43% among all CD patients[4]. PFCD usually exhibits a complex clinical presentation that leads to persistent manifestations like continuous pus, pain, uncomfortable sitting posture, and fecal leakage. In addition, the severity of PFCD is associated with CD course and is the predictive factor of CD patients' long-lasting poor prognoses[5]. These clinical features can further cause work disability, frequent admission, and psychological, sex, and social problems that significantly deteriorate a patient's quality of life and lead to severe psychological impacts.

A study conducted by Mahadev *et al*[6] showed that 73% of PFCD patients were experiencing symptoms of depression. Remarkably, 13% of those had a strong tendency to suicide and were even willing to trade their lifespan (over 10%) for PFCD relief. To further investigate the prevalence of depression in CD patients, there was a cohort study[7] regarding perianal lesions as essential predictors of CD patients with depression. The prevalence of perianal lesions in CD patients with depression was almost two-fold greater than in patients without CD.

Another investigation[8] demonstrated that perianal lesions were the main factor of both depression and anxiety. In addition, CD patients with depressive and anxiety disorder comorbidities had a triple occurrence rate of perianal lesions and surgical procedure rate in comparison with the CD patients without the above psychological disorders. Moreover, a notable relationship was noted between psychological diseases and CD[9]. The link possesses the possibility of CD exacerbations or other complications, therefore aggravating the healthcare-related economic burden. Thus, it is imperative to prioritize psychological issues in patients with PFCD and monitor the possible related risk factors.

Psychological disorders in IBD were shown to be independently associated with female sex, disease activity, and ostomy in previous research[10,11]. However, there is a scarcity of analogous studies focusing on specific disease types of IBD. In contrast to general CD patients, those with perianal lesions experience distinct and additional symptoms that substantially alter their disease experience. Furthermore, research on the factors of depression in this specific subset of PFCD patients is limited at present. In short, we conducted a cross-sectional study to screen the depressive symptoms of PFCD patients and examined the related clinical factors to determine the research deficiencies of IBD-related psychological issues.

MATERIALS AND METHODS

Subjects

Patients with PFCD who were admitted to the anorectal ward of the Affiliated Hospital of Nanjing University of Traditional Chinese Medicine and diagnosed by perianal magnetic resonance imaging (MRI) during the period from September 2022 to September 2023 were included in this study consecutively. Prior to the enrollment, written informed consent was obtained from the subjects or their legal guardians. The study was approved by the Affiliated Hospital of Nanjing University of Chinese Medicine (Approval No. 2020NL-170-02).

Patients were considered for enrollment if they fit the following inclusion criteria: (1) Diagnosed by perianal MRI; (2) age between 16 years and 60 years; (3) minimum 6 years of education; and (4) basic reading and cell phone operation skills. Exclusion criteria were as follows: (1) Diagnosed with psychiatric disorders explicitly; (2) unable to understand the content in the questionnaire; (3) clinical data missing and not being able to be communicate; and (4) without any perianal MRI examination.

Data collection and extraction

In our study, data collection, including demographic and clinical information, was conducted by a questionnaire and professional IBD medical staff. All data were collected and organized within 1 wk of admission to the anorectal ward.

The following information was gathered through a uniform questionnaire: (1) Basic demographic information including age, sex, body height, weight, smoking history, marital and reproductive status, educational level, employment status, and income level; and (2) physiologic and psychological assessment by using the Patient Health Questionnaire-9 (PHQ-9), IBD Patient Quality of Life Questionnaire (IBDQ), and IBD Fatigue (IBD-F) Patient Self-assessment Scale. Specialized IBD medical staff registered the following variables: (1) Medical history and characteristics of CD involving the Montreal classification, CD course, gastrointestinal surgery history, ostomy history, CD Activity Index (CDAI) score and medication history; (2) laboratory inflammation indicators including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin (FC); and (3) medical history and features of perianal disease covering PFCD course, perianal surgery history, Perianal Disease Activity Index (PDAI), Wexner Score, and modified Van Assche index. The modified Van Assche index was assessed by two or more radiologists specializing in the field of proctology to minimize errors in the analysis.

Measurements and instruments

PHQ-9: Our study utilized the PHQ-9 as a tool for evaluating the depressive symptoms of PFCD patients. The scale is a nine-item self-reported questionnaire and has emerged as the most dependable tool for detecting depression[12] because of its perfect sensitivity and specificity[13]. The scoring system of the PHQ-9 is as follows: Scores of 0-4 correspond to the absence of depression; scores of 5-9 correspond to mild depression; scores of 10-14 correspond to moderate depression; scores of 15-19 correspond to moderately severe depression; and scores of 20-27 correspond to severe depression.

IBDQ: We used the Chinese version of IBDQ to evaluate the quality of life among PFCD patients. This assessment encompasses not only gastrointestinal symptoms but also constitutional symptoms, social functioning, and emotional state. The total score of the IBDQ ranges from 32 to 224, with higher scores indicating a higher quality of life. The questionnaire demonstrated adequate validity and reliability[14].

IBD-F patient self-assessment scale: Czuber-Dochan *et al*[15] invented a self-assessment scale for IBD patients, which has good reliability and validity, and can be used as an initial screening tool for fatigue in IBD patients. The first part of the Chinese version of the IBD-F scale was used in this study to assess the level of fatigue in PFCD patients. The relevant scale in our study is as follows: No fatigue (0 points); mild to moderate fatigue (1-10 points); and severe fatigue (11-20 points).

Modified van assche index: This study applied the perianal modified Van Assche index to objectively quantify the disease activity of fistulizing inflammation. In 2017, Samaan *et al*[16] amended the original Van Assche index[17], detailed the standardized score definition in each entry item, and improved the inter-rater reliability. The score was evaluated by two or more radiologists specializing in the field of proctology in our study. A higher total score indicated a more severe perianal inflammatory activity.

Statistical analysis

The statistical analyses were performed with SPSS 26.0 software (IBM Corp., Armonk, NY, United States). The measurement data were represented by mean ± standard deviation if they obeyed normal distribution, and the group data

were compared using the independent sample *t*-test. In contrast, those not obeying normal distribution were analyzed by the Wilcoxon rank-sum test based on the description of the median ± interquartile range. Counting data were expressed as number of cases and percent, and Fisher's exact probability method was applied for comparison between groups.

A logistic regression model was utilized to conduct a multivariate analysis. The outcomes were presented as odds ratios (ORs) and corresponding 95% confidence intervals (CI). Variables with *P* values < 0.10 in the univariate analysis were further analyzed in the multivariate analysis. The factors that showed statistical significance in the multivariate analysis were further subjected to Spearman rank correlation analysis to examine the relationship between the severity of depression and those variables. Furthermore, multiple linear regression analyses were conducted to ascertain the potential relationship between the demographic and clinical features of the cohort and the severity of depression.

The statistical methods of this study were reviewed by Jun-Qin Wang from the Department of Public Health, Nanjing University of Chinese Medicine.

RESULTS

General population information and clinical data

This research comprised a cohort of 123 PFCD patients eligible for enrollment. Of these patients, 85 (69.11%) were male and 38 (30.89%) were female. The age of the patients ranged from 16 years to 59 years, with a mean age of 28.55 ± 9.18 years. Almost one-third were married (36.59%), had a high school education or above (69.93%), and were employed (59.35%). An average CD duration of 4.26 ± 4.70 years and an average PFCD duration of 6.00 ± 23.00 months were shown. The majority of the lesions were located in the ileum (42.28%) among the study population, and 71.54% of the population used biologics. More detailed demographic data and clinical features are summarized in Table 1.

Prevalence of depression among PFCD patients

As for the depression levels among 123 participants, 70 of them displayed depressive symptoms. To be specific, 53 patients exhibited mild depression (43.09%), 6 patients exhibited moderate depression (4.88%), 8 patients exhibited moderately severe depression (6.50%), and 3 patients exhibited severe depression (2.44%) (Table 2).

Analysis of influencing factors associated with depression in PFCD patients

Univariate analysis: The patients with PFCD were categorized into two groups: Those with depression and those without depression. The analysis of clinical data of both groups of patients showed that the use of ESR, CRP, FC, CDAI score, PDAI score, Wexner score, modified Van Assche index, IBDQ score, and IBD-F score between the depressive group and the non-depressive group had significant statistical differences *(P* < 0.05*)* (Table 1).

Multivariate logistic regression analysis: The possible factors (variables which adhered to *P* < 0.10 in Table 1) related to depressive symptoms were screened, and a multivariate logistic regression analysis was performed. The most obvious finding to emerge from this analysis was that the modified Van Assche index (OR = 1.24, 95%CI: 1.01 to 1.53), PDAI score (OR = 0.69, 95%CI: 0.50 to 0.95), IBDQ score (OR = 0.93, 95%CI: 0.88 to 0.97), and IBD-F score (OR = 1.72, 95%CI: 1.23 to 2.42) significantly influenced the prevalence of depression (*P* < 0.05) (Table 3 and Figure 1).

Spearman rank correlation analysis: The PDAI score, IBDQ score, perineal modified Van Assche index, IBD-F score, and the severity of depression were analyzed using Spearman rank correlation analysis. The analysis showed the following conclusions: (1) A lower IBDQ score was associated with more severe depression (*r* = -0.711, *P* = 0.000); (2) a higher modified Van Assche score was associated with more severe depression (*r* = 0.466, *P* = 0.000); (3) a higher IBD-F score was associated with more severe depression (*r* = 0.593, *P* = 0.000); and (4) a higher PDAI score was associated with more severe depression (*r* = 0.333, *P* = 0.000). The relationship between depressive level and the above variables was presented using box plots (Figure 2).

Multiple linear regression analysis: The increased modified Van Assche score (*β* value = 0.166, 95%CI: 0.02 to 0.31) and the decreased IBDQ score (*β* value = -0.116, 95%CI: -0.14 to -0.09) were independently associated with the severity of depression. These factors explained the variance of 65.0% (Table 4).

DISCUSSION

Our cross-sectional study revealed a significant prevalence of depressive symptoms among PFCD patients in which 56.91% of them were in distress. It is noteworthy that even 13.82% of them exhibited moderate to severe levels of depression. Risk factors of depression in CD patients were shown to be linked with the activity of perianal lesions, quality of life, and fatigue. To the best of our knowledge, this study was one of the few studies about the prevalence of depression among PFCD patients and the related factors. Furthermore, our analysis encompassed various variables that might be directly associated with depression, including the course of perianal lesions, frequency of perianal surgeries, the modified Van Assche score, quality of life, and fatigue. Notably, unique characteristics of the perianal condition were examined infrequently in prior studies.

Table 1 Demographic and clinical characteristics of perianal fistulizing Crohn's disease patients with and without depression, *n* (%)

Variable	Cohort, *n* = 123	Without depression, *n* = 53	With depression, *n* = 70	*P* value
Demographic characteristics				
Female sex	38 (30.89)	12 (22.64)	26 (37.14)	0.115
Age in yr	28.55 ± 9.18	28.51 ± 9.17	28.59 ± 9.26	0.964
BMI in kg/m^2	21.02 ± 3.85	21.56 ± 3.80	20.60 ± 3.86	0.175
Smoker	9 (7.32)	1 (1.89)	8 (11.43)	0.076
High school or above	86 (69.93)	41 (77.36)	45 (64.29)	0.164
Married	45 (36.59)	20 (37.74)	25 (35.71)	0.852
Procreated	38 (30.89)	15 (28.30)	23 (32.86)	0.694
Currently employed	73 (59.35)	32 (60.38)	41 (58.57)	0.855
Low-income population as ≤ 3.6 million yuan	61 (49.59)	27 (50.94)	34 (48.57)	0.856
Overall clinical characteristics				
CD course in yr	4.26 ± 4.70	3.90 ± 4.10	4.53 ± 5.11	0.465
CD phenotypes				
L1-Terminal ileum	52 (42.28)	25 (47.17)	27 (38.57)	0.362
L2-Colon	33 (26.83)	16 (30.19)	17 (24.29)	0.539
L3-Ileum and colon	38 (30.89)	12 (22.64)	26 (37.14)	0.115
B2-Stricturing	39 (31.71)	18 (33.96)	21 (30.00)	0.698
B3-Penetrating	3 (2.44)	2 (3.77)	1 (1.43)	0.577
CDAI score, median ± IQR	98.77 ± 119.39	46.67 ± 82.04	130.20 ± 99.21	0.000
History of gastrointestinal surgery	18 (14.63)	6 (11.32)	12 (17.14)	0.445
History of ostomy	8 (6.50)	5 (9.43)	3 (4.29)	0.289
Laboratory indicators, median ± IQR				
ESR in mm/h	23.00 ± 29.00	14.00 ± 22.00	34.00 ± 39.00	0.000
CRP in mg/L	7.96 ± 17.80	5.72 ± 11.57	10.20 ± 25.47	0.004
FC in μg/g	732.80 ± 1128.30	374.20 ± 845.00	836.90 ± 1414.95	0.001
Current medication				
Biologics therapy	88 (71.54)	35 (66.04)	53 (75.71)	0.313
Immunomodulator therapy	26 (21.14)	8 (15.09)	18 (25.71)	0.184
Corticosteroid therapy	15 (12.20)	5 (9.43)	10 (14.29)	0.580
Perianal clinical characteristics				
PFCD course in month, median ± IQR	6.00 ± 23.00	5.00 ± 24.00	7.50 ± 28.00	0.146
History of perianal surgery of ≥ 2	57	24	33	0.857
PDAI score, median ± IQR	6.00 ± 5.00	4.50 ± 5.00	6.00 ± 5.00	0.001
Wexner score, median ± IQR	2.00 ± 7.00	1.00 ± 4.00	4.50 ± 7.00	0.001
Modified Van Assche index, median ± IQR	12.00 ± 8.00	8.00 ± 11.00	13.00 ± 5.00	0.000
Physiological and psychological characteristics				
IBDQ score, median ± IQR	172 ± 50	194 ± 27	152 ± 37	0.000
IBD-F score, median ± IQR	6.00 ± 5.00	4.00 ± 5.00	8.00 ± 4.00	0.000

BMI: Body mass index; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; FC:

Fecal calprotectin; IBD-F: Inflammatory Bowel Disease Fatigue; IBDQ: Inflammatory Bowel Disease Patient Quality of Life Questionnaire; IQR: Interquartile range; PDAI: Perianal Disease Activity Index; PFCD: Perianal fistulizing Crohn's disease.

Table 2 Prevalence of depression among perianal fistulizing Crohn's disease patients, *n* (%)

Clinical characteristic	No depression	Mild depression	Moderate depression	Moderately severe depression	Severe depression
PFCD	53 (43.09)	53 (43.09)	6 (4.88)	8 (6.50)	3 (2.44)

PFCD: Perianal fistulizing Crohn's disease.

Table 3 Multivariate logistic regression analysis of perianal fistulizing Crohn's disease patients with depression

Factor	*β* value	Wald value	*P* value	OR value	95%CI
Smoker	1.111	0.36	0.550	3.04	0.08 to 116.33
CDAI score	0.000	0.00	0.957	1.00	0.99 to 1.02
ESR in mm/h	0.029	2.20	0.138	1.03	0.99 to 1.07
CRP in mg/L	-0.030	1.28	0.258	0.97	0.92 to 1.02
FC in μg/g	0.001	3.17	0.075	1.00	1.00 to 1.00
PDAI score	-0.373	5.03	0.025	0.69	0.50 to 0.95
Wexner score	0.020	0.04	0.850	1.02	0.83 to 1.26
Modified Van Assche index	0.218	4.37	0.037	1.24	1.01 to 1.53
IBDQ score	-0.076	9.73	0.002	0.93	0.88 to 0.97
IBD-F score	0.545	10.02	0.002	1.72	1.23 to 2.42

CI: Confidence interval; CDAI: Crohn's Disease Activity Index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; FC: Fecal calprotectin; IBD-F: Inflammatory Bowel Disease Fatigue; IBDQ: Inflammatory Bowel Disease Patient Quality of Life Questionnaire; OR: Odds ratio; PDAI: Perianal Disease Activity Index.

Table 4 Multiple linear regression analysis of perianal fistulizing Crohn's disease patients with depression

Factor	*β* value	*t* value	*P* value	95%CI	R^2
Smoker	0.124	0.09	0.928	-2.58 to 2.83	0.650
CD activity index	0.006	0.96	0.341	-0.01 to 0.02	
ESR in mm/h	0.005	0.25	0.804	-0.03 to 0.04	
CRP in mg/L	-0.006	-0.32	0.746	-0.04 to 0.03	
FC in μg/g	0.000	0.78	0.440	0.00 to 0.00	
PDAI score	-0.134	-1.06	0.292	-0.39 to 0.12	
Wexner score	-0.069	-0.88	0.380	-0.23 to 0.09	
Modified Van Assche index	0.166	2.22	0.028	0.02 to 0.31	
IBDQ score	-0.116	-8.58	0.000	-0.14 to -0.09	
IBD-F score	0.169	1.61	0.109	-0.04 to 0.38	

CI: Confidence interval; CD: Crohn's disease; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; FC: Fecal calprotectin; IBD-F: Inflammatory Bowel Disease Fatigue; IBDQ: Inflammatory Bowel Disease Patient Quality of Life Questionnaire; PDAI: Perianal Disease Activity Index.

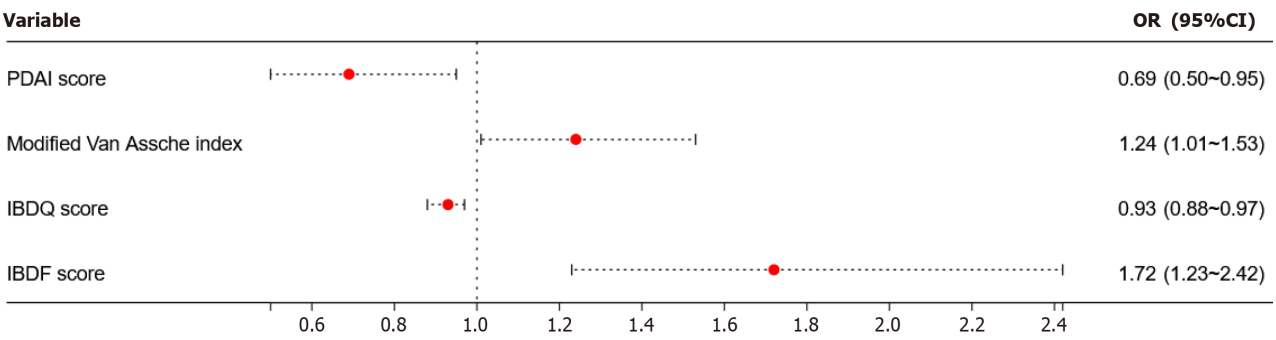

Figure 1 Factors associated with the presence of depression in patients with perianal fistulizing Crohn's disease. PDAI: Perianal Disease Activity Index; IBDQ: Inflammatory Bowel Disease Patient Quality of Life Questionnaire; IBDF: Inflammatory Bowel Disease Fatigue; OR: Odds ratio; CI: Confidence interval.

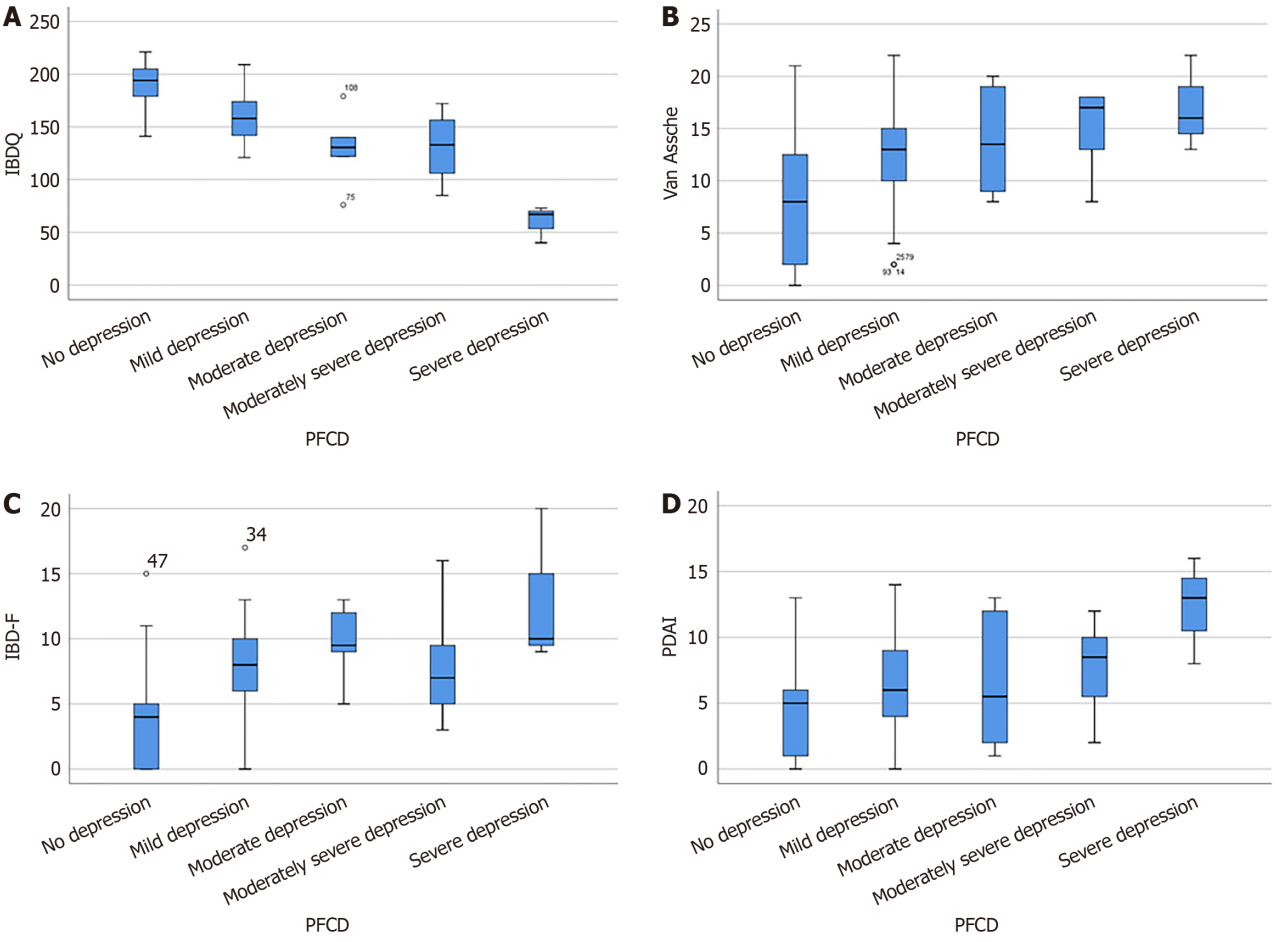

Figure 2 Relationship between the severity of depression and variables. A: Inflammatory Bowel Disease Patient Quality of Life Questionnaire score; B: Modified Van Assche index; C: Inflammatory Bowel Disease Fatigue score; D: Perianal Disease Activity Index score. PFCD: Perianal fistulizing Crohn's disease; PDAI: Perianal Disease Activity Index; IBDQ: Inflammatory Bowel Disease Patient Quality of Life Questionnaire; IBD-F: Inflammatory Bowel Disease Fatigue.

The prevalence of depressive symptoms was markedly greater in patients with PFCD compared to those with typical CD and IBD. Two meta-analyses[1,11] determined that the occurrence rate of depressive symptoms in IBD patients was around 25.2% and 21.6%, respectively. Likewise, the occurrence rate of depression in CD patients varied from 17.5% in a survey based on a primary care database in the United Kingdom to 41.7% in a different study that examined a population-based group[18,19]. The existing findings on the prevalence of depression in IBD were still multiform. It might be attributed to factors such as sample size, geographical and age disparities within the study population, and the selection of the depressive rating scale.

The findings of our study exhibited a notable increase compared to the prior studies. This distinction may be due to the fact that our investigation specifically focused on PFCD. Patients with PFCD exhibit diverse disease manifestations compared to those without perianal fistulas. They suffer from challenging therapeutic dilemmas and alterations of body

image and living habits, exacerbating life quality and psychological consequences due to persistent defecation, suppuration, pain, infection, and impairments in the sphincter and perineal tissues. In addition, this discrepancy could be linked to the different applications of psychological assessment instruments. When comparing with the structured diagnostic interviews (gold standard clinical diagnosis) of depression, there was a possibility of overestimating symptoms referred to the PHQ-9 self-reported scale. Nevertheless, our study revealed a significant prevalence of depressive symptoms in CD patients, particularly in a specific subset of patients with PFCD, where mental health issues play a crucial role.

Previous literature had reported a higher occurrence rate of depression among patients in active CD state compared to those in remission state[20], and the overall increased disease activity was independently associated with the development of depression[21,22]. However, we did not find any correlation between the prevalence of depression and disease activity indicators (CDAI score and inflammatory factors like FC, ESR, and CRP). This might be ascribed to the patient population in this study, which was mainly diagnosed with PFCD with low overall disease activity. This study also disclosed that two indicators of perianal disease activity, the PDAI score and the modified Van Assche score, were the main factors associated with depression in PFCD. In particular, the modified Van Assche score, an objective MRI indicator, showed statistically significant results in multivariate logistic and multiple linear regression analysis, making the results more reliable.

A case-control study including more than 1300 patients revealed that perianal disease was a significant risk factor for anxiety and depression in patients with IBD[7]. Another investigation also documented that history of perianal disease was the major risk factor for anxiety and depression in CD patients[8]. Not surprisingly, all of the studies mentioned above involved perianal disease history as their experimental criteria without quantifying the perianal disease activity. Our present study utilized two quantitative indicators for evaluating perianal fistulizing activity and the modified Van Assche score, which expressed the existence of a correlation between perianal activity and depression. Higher perianal inflammatory activity is associated with more complex fistulas, more secretions, swelling, and pain and is accompanied by an uncomfortable sitting posture, unpleasant odor, low self-esteem, and feelings of embarrassment, thus increasing the risk of depression. In order to detect depressive disorder in PFCD patients, physicians should go beyond laboratory parameters in clinical practice since inflammatory markers that react to disease activity do not correlate with depression. Perianal MRI is particularly important.

CD patients with perianal comorbidities such as perianal abscesses and fistulas have a lower quality of life than the general population[23]. The delayed healing and intractable nature of PFCD means that patients often experience uncomfortable symptoms and the impacts of repeated surgeries, disrupting their daily life, relationships, social participation, and psychological well-being, which may lead to a lower quality of life. In this study, we found that the life quality of PFCD patients with depressive symptoms was lower than that of those without depressive symptoms. This is similar to the findings of García-Alanís *et al*[24].

In the multivariate regression analysis, a reduction in quality of life was significantly associated with the presence and severity of depression. A lower IBDQ score was associated with a more severe depression. Geiss *et al*[21] reported a strong correlation between life quality and PHQ-9 score among IBD patients. The IBDQ score used in this research incorporated the impact of the disease on psychological functioning and, to some extent, overlapped with patients' psychoemotional evaluations, which may partly explain the stronger correlation between life quality and depression. Poor quality of life will aggravate psychological distress, such as anxiety and depression, in patients with IBD[25]. A lower quality of life is manifested in anxiety about the loss of bowel control, worry about systemic symptoms, fear of socialization, stress from not being able to work and study normally, and a lack of confidence in body image, which will contribute to an increasing risk of depression.

Fatigue coexists with psychosomatic problems such as depression and anxiety in chronic conditions[26,27], including IBD[28]. Our findings suggested that fatigue was significantly associated with the presence of depression in PFCD, which might have the same behavioral, emotional, and cognitive characteristics. The main symptom of fatigue is a lack of energy or persistent tiredness that is disproportionate to physical exertion, limiting daily activities, and not being able to be relieved by rest[29]. CD patients have a higher prevalence of fatigue[30]. They describe fatigue as one of the most bothersome symptoms[31] and may even be more debilitating and depressing than CD symptoms. This trouble severely affects patient quality of life and reduces labor productivity. Jonefjäll *et al*[32] found that fatigue could have a negative psychological impact on IBD patients, exacerbating clinical symptoms and promoting disease progression. Another study also showed that concurrent depression was the most substantial risk factor of IBD with fatigue[33]. These findings complement our results and suggest that there may be complex interactions and interdependencies between depression and fatigue.

Age, smoking history, education level, marital status, annual income, and related medication were not associated with depression in PFCD according to our research. Being female had been reported as a predictor of depression in patients with IBD in several papers[34,35], and previous abdominal surgeries and ostomy had also been reported to be associated with depression in perianal CD patients[6]. Our findings, however, did not show any significant association between depression and sex or abdominal surgery treatment. This might be related to the small sample size and heterogeneity of participants in our study.

We included, for the first time, three parameters regarding the characteristics of perianal disease, namely the PFCD course, the number of perianal surgeries and the Wexner score, which can reflect the chronic course and severity of anal fistula in patients. However, we were puzzled when the three perianal parameters did not significantly intensify depression as we had hypothesized they would, and the longer intervals between fistula recurrences and surgeries might overestimate the duration of PFCD and the number of perianal surgeries. In addition, the overall Wexner score was low, and anal incontinence was not that critical in our study population.

Our analyses had some limitations. First, the sample size of our study was relatively small. Further extensive sample size studies are necessary to screen for the prevalence of depression in PFCD patients more accurately and to identify risk further factors for depression. Second, the IBDQ was used in this study to assess the overall quality of life of CD patients, but it did not allow for a comprehensive assessment of the impact of fistula. The Crohn's Anal Fistula Quality of Life scale [36] is a brand-new measurement tool for complex PFCD. In the future, we can use it to evaluate the quality of life of PFCD patients, and the results may be more meaningful. Furthermore, none of the patients enrolled in this study underwent antidepressant psychotherapy although they were exhibiting diverse levels of depressive symptoms. This condition could potentially stem from the limited awareness of depression associated with PFCD among medical professionals and patients. Moving forward, we are committed to broadening our research scope and conducting comparative analyses on the alterations in prior and post antidepressant therapy, thereby enhancing the specificity of our study. Finally, there may be an interconnection between depression, quality of life, and fatigue, necessitating further studies to test causal and more complex models of depression related to PFCD.

CONCLUSION

In conclusion, our study suggested that patients with PFCD had a higher prevalence of depression, and the related risk factors of depression included the PDAI score, the modified Van Assche score, quality of life, and fatigue. The above suggestion may help physicians to emphasize, accurately identify, and encourage high-risk groups for psychological disorders, thus alleviating patients' symptoms and improving quality of life and prognosis.

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FOOTNOTES

Author contributions: Li J and Ng WY contributed equally to design the studies, writing, and statistical analysis, and should be considered as co-first authors; Wang ZQ and Yang BL contributed to project, manuscript writing, review, and revision; Yuan F and Lan X generated figures and tables according to the analysis; Qiao LC and Zhu LB performed subject and data collection; all authors were involved in the critical review of the results and have contributed to, read, and approved the final version of the manuscript. The reasons for designating Wang ZQ and Yang BL as co-corresponding authors are listed below: The research was conducted as a joint undertaking, with the shared authorship status accurately representing the equal distribution of duties and workload involved in the study and the preparation of the manuscript. This arrangement facilitates efficient communication and handling of matters after submission, thereby elevating the overall quality and dependability of our study. By naming these researchers as co-corresponding authors, we acknowledge and celebrate their equitable input, as well as the collaborative and team-oriented essence of the study. In essence, we assure that specifying Wang ZQ and Yang BL as co-corresponding authors is appropriate for our submission, as it accurately embodies our team's collaborative ethos, balanced contributions, and diversity.

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ORIGINAL ARTICLE

Observational Study

Need for education of psychiatric evaluation of offenders with mental disorders: A questionnaire survey for Japanese designated psychiatrists

Akihiro Shiina, Tomihisa Niitsu, Masaomi Iyo, Chiyo Fujii

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Abstract

BACKGROUND

The management of offenders with mental disorders has been a significant concern in forensic psychiatry. In Japan, the introduction of the Medical Treatment and Supervision Act in 2005 addressed the issue. However, numerous psychiatric patients at risk of violence still find themselves subject to the administrative involuntary hospitalization (AIH) scheme, which lacks clarity and updated standards.

AIM

To explore current as well as optimized learning strategies for risk assessment in AIH decision making.

METHODS

We conducted a questionnaire survey among designated psychiatrists to explore their experiences and expectations regarding training methods for psychiatric assessments of offenders with mental disorders.

RESULTS

The findings of this study's survey suggest a prevalent reliance on traditional learning approaches such as oral education and on-the-job training.

CONCLUSION

This underscores the pressing need for structured training protocols in AIH consultations. Moreover, feedback derived from inpatient treatment experiences is identified as a crucial element for enhancing risk assessment skills.

Key Words: Forensic psychiatry; Administrative involuntary hospitalization; Psychiatric assessment; Risk assessment; Mental disorders; Training protocols; Clinical practice; Structured learning; Feedback mechanisms; Program development

Core Tip: In this study, we clarified that many Japanese psychiatrists rely on traditional learning approaches such as oral education and on-the-job training for learning risk assessment skills. Some structured training protocols as well as feedback derived from inpatient treatment experiences are needed for improving skills of practitioners engaging in administrative involuntary hospitalization.

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INTRODUCTION

The management of offenders with mental disorders has been a longstanding focus of discussion among general and forensic mental health specialists. Numerous experts acknowledge that solely punishing offenders is unlikely to deter recidivism, particularly in cases where the offense stems directly from psychiatric symptoms. Instead, there is a consensus that appropriate psychiatric treatment is necessary to facilitate their reintegration into society[1,2].

As a result, most legal systems and societies require the establishment of criminal responsibility before imposing sanctions on offenders. Those who commit crimes while deemed legally insane as a result of mental disorders are typically exempt from punishment. This principle is widely regarded as rational in most developed countries, for several reasons[3].

With regards to Japanese legislation, an act of insanity is not punishable, and an act of diminished responsibility shall lead to punishment being reduced, according to Article 39 of the Penal Code. Insanity is defined by the Supreme Court as the inability to recognize the disparity between good and evil as well as control oneself as a result of mental disorders. Diminished responsibility is defined as a state in which these abilities are strongly impaired as a result of mental disorders. However, for many years, Japan had no specific legal provisions for offenders with mental disorders. They were treated under the Mental Health and Welfare Act.

Post-debate, the Act on Medical Care and Treatment for Persons Who Have Caused Serious Cases under the Condition of Insanity (abbreviated to the Medical Treatment and Supervision Act, or MTS Act) was enacted in 2005, coinciding with the widespread reform of the Japanese forensic mental health system[4]. Under this new scheme, individuals committing a serious criminal offense while insane or having diminished responsibility are dealt with within a judicial and administrative framework. The enactment of the MTS Act also meant that clinical psychiatrists would have the opportunity to collaborate with legal professionals, such as judges and lawyers in the treatment of offenders. Additionally, judges faced the necessity of learning about clinical psychiatry for appropriate decision-making under the MTS Act.

Conversely, offenders who are not identified as not guilty by reason of insanity or as having diminished responsibility are treated the same as in the past. In addition, offenders who committed less serious crimes under the influence of mental disorders were not subjected to the MTS Act. Both can be considered to be subjected to an administrative involuntary hospitalization (AIH) scheme that was established in 1950. This scheme was succeeded by the Mental Health and Welfare Act (amended in 2013) without any major alterations. Under this scheme, if an individual is recognized as being at risk of harming themselves or others as a result of a mental disorder, the police and prosecutor report the case to the prefectural governor. The governor can then order the individual to be hospitalized in a designated psychiatric hospital based on an assessment by two designated psychiatrists that involuntary hospitalization is necessary[5].

However, legislation regarding the content of treatment under AIH by the prefectural governor's order is scarce. In addition, compared to the scheme of the MTS Act, AIH has rarely been discussed, even in academia. There are few published national reports on the performance and outcomes of AIH. In particular, the standard for inducing the AIH scheme is too vague to be appropriately managed. The Ministry of Health, Labour and Welfare published an official notice regarding the standard of AIH in 1961, as "Guidelines for Handling Administrative Involuntary Hospitalization and Consent Hospitalization for Patients with Mental Disorder". Although the scheme of Consent Hospitalization was abolished in 1988, the AIH standard described in this article is still in effect. This standard should be criticized as being outdated. For instance, psychopathy has been illustrated as an example of AIH. However, most Japanese psychiatrists and police officers believe that psychopathic offenders should be punished for their crimes as opposed to being hospitalized involuntarily into psychiatric hospitals.

Furthermore, the criteria for determining whether patients should undergo AIH remain unclear. In Japan, the proficiency in psychiatric assessment of offenders with mental disorders, particularly for establishing criminal responsibility in court trial, has garnered significant attention among specialists. While training seminars on psychiatric assessment are held several times a year, the focus on AIH-related skills, including risk assessment and patient management, has been largely overlooked since the inception of the AIH scheme in the 1950s. To our knowledge, there exists only one textbook authored by Nishiyama[6] in 1984 that outlines the consultation method for AIH cases. Moreover, there is a notable absence of lectures or seminars aimed at equipping professionals with the necessary skills to effectively evaluate patients in AIH decision-making sessions.

In the United Kingdom, forensic psychiatrists take a three-year course prior to gaining a status of a consultant. It includes a professional program with peer groups to learn how to assess and manage the risk of harm self or others in patients with mental disorder. In the United States, they take two-year fellowship program post completing residency in general psychiatry[7]. In contrast, there is no structured training course for forensic psychiatrists in Japan, while psychiatric examination for evaluating.

Considering this situation, there is a need for educational materials to assist young psychiatrists with efficiently learning the points to be considered by designated psychiatrists when they conduct diagnostic examinations for AIH in current psychiatric practice.

For the initial step in accomplishing the goal described above, a questionnaire survey of designated psychiatrists who are currently providing AIH consultation was conducted to obtain their opinions on the actual conditions of medical examinations and education on medical examinations as well as elucidate the expert consensus on the procedures and the need for medical examination training in the situation of AIH consultation.

In this study, the aim was to explore the resources utilized by practicing psychiatrists to enhance their skills in risk assessment of subjects undergoing AIH. Additionally, elucidating the perspectives of psychiatrists regarding the most effective methods for learning about psychiatric evaluations of such patients was included.

MATERIALS AND METHODS

Study overview

This study utilized a mail-based questionnaire survey of Japanese psychiatrists to clarify the current experience and future needs of the methods of education for psychiatric assessment with regards to offenders with mental disorders.

Criteria for participation

Psychiatrists belonging to a psychiatric hospital (either the public sector or the private sector) with a license of a designated psychiatrists were recruited as participants of the study. Psychiatrists of any gender, age, and ethnicity were welcomed, but participants were over 29 years old as a result of obtaining a designated psychiatrist license required at least 5 years of experience as a medical doctor. Individuals who had already been involved in this study or preceding studies at the start of this study were excluded.

Measure

We constructed a series of questionnaires written by Japanese post-discussion with an expert panel composed of research members who were leading psychiatrists. Several studies regarding this issue were referred to, as well as reports of relevant research published in the past[7,8]. In general, there are two ways to acquire new job skills: to learn knowledge by reading materials or attending seminars organized by experts, or to learn from professionals while practicing the skills on-the-job. Seminars regarding national legislation are often held by the government or related organizations. Conversely, Japan does not have a structural scheme in place for on-the-job training in the field of the AIH. Instead, several psychiatrists attended the consultation of other designated psychiatrists. Attendance at a designated psychiatrist's examination is one possible way to learn about the AIH skills[9]. In addition, the Expert Panel also discussed the possibility of improving the skills by learning more about the condition of inpatients at the designated hospitals in which they will be treated post-decision of the AIH. Based on these discussions, the ten types of ways for learning AIH examination skills were identified.

The questionnaire included options for learning about the risk assessment of offenders with mental disorders. The participants were asked to answer whether they had previously utilized these learning methods. They were also asked to evaluate the appropriateness of each method on a 9-point Likert scale. Furthermore, we gathered the participants' working records (*e.g.*, years of practice as a designated psychiatrist and number of cases they experienced for the evaluation in this year), as exhibited in Supplementary material.

Sending questionnaire

In this study, our aim was to investigate the resources utilized by practicing psychiatrists to improve their skills in risk assessment for subjects undergoing AIH. Additionally, we sought to elucidate psychiatrists' perspectives on the most effective methods for learning about psychiatric evaluations of such patients.

Statistical analyses

We statistically analyzed the data utilizing the SPSS for Windows version 28 (IBM, Armonk, NY, United States).

Firstly, each participant's background data for presenting descriptive statistics was analyzed. Subsequently, the mean and 95%CI were calculated. A categorical rating of first-line, second-line, or third-line options were designated based on the lowest category in which the CI fell, with boundaries of 6.5 or greater for the first-line (preferred) options, 3.5 or greater but less than 6.5 for the second-line (alternate), and less than 3.5 for the third-line (usually inappropriate) options, respectively. Among the first-line options, the option referred to as "best recommendation/essential" was defined, which approximately 50% of the experts rated it 9. This analysis method was adopted after referring to an expert consensus series of guidelines. Finally, we conducted additional analyses to clarify the disparities in opinions between the groups of respondents. The level of significance in each analysis was established at $P < 0.05$.

Ethical issues

The study protocol was approved by the Ethics Committee of Chiba University Graduate School of Medicine with the No. 1145, Dec 14, 2020. The survey was conducted anonymously by the researchers. Participants were considered to have provided informed consent to participate in the study when they returned the answer sheet. This study was registered in the UMIN Clinical Trials Registry (UMIN number 000047167).

RESULTS

General statistics

The survey was conducted from May 2021 to February 2022. We distributed the questionnaire to a total of 1290 hospitals (93 public and 1197 private). Out of these, we received 571 answer sheets (183 from public hospitals, 380 from private hospitals, and 8 with unknown origins). Since the official count of designated psychiatrists in Japan is undisclosed, the response rate cannot be determined. However, according to records from 2022, there were a total of 3500 seats available for designated psychiatrists to attend official seminars (https://www.shiteii.com/update.php). Every designated psychiatrist in Japan is mandated to attend a seminar every five years. Based on this, it is estimated that there are approximately 17,500 actively practicing designated psychiatrists. Therefore, we estimate that our survey captured opinions from approximately 3.3% of all designated psychiatrists in Japan.

General background of the respondents

The age of the respondents was 51.27 ± 11.07 years. The main characteristics of the respondents were as follows: Public hospital, 183; private hospital, 380; outpatient section of a general hospital without psychiatric beds, 2; outpatient clinic, 3; university and education/research facility, 2; and others, 1.

The primary psychiatric specialties were as follows: General psychiatry, 430; emergency psychiatry, 70; forensic mental health, 14; other psychiatric specialties, 22; education/research, 1; administration/management, 25; and others/invalid answers, 8. The mean years of psychiatric practice were 22.29 ± 11.79 years, with designated psychiatrists having 16.31 ± 10.88 years.

Number of cases of AIH consultation

The numbers of cases of AIH consultation the respondents had conducted prior are exhibited in Figure 1. The mean number of AIH consultations per respondent in the latest year was 2.93 ± 3.96.

Methods of learning AIH consultation skills that respondents experienced

Ten learning methods were suggested to the respondents. Consequently, numerous psychiatrists have learned AIH consultation skills in several ways. The most common ways were through lectures from a supervisor/employer or senior psychiatrists, as well as learning through medical treatment of a patient who was subjected to AIH. Less than 10% attended an official seminar besides those mandatory to maintain the designated psychiatrist license. The detailed results are listed in Table 1 and Figure 2.

Ideas of optimal ways to learn AIH consultation skills

Each option was evaluated by the respondents utilizing a 9-point Likert scale. As a result, seven of the ten options were defined as the first-line according to the criteria suggested in the method section. Meanwhile, "Asking for advice from a senior psychiatrist exhibiting the subject's information prior to conducting the consultation", "Consulting with another designated psychiatrist", and "Asking for comments from a senior psychiatrist and exhibiting them with your report post the AIH consultation" were categorized as second-line options. None of the items were defined as the "best recommendation/essential". The results are exhibited in Figure 3.

Additional analyses

We conducted two additional analyses to interpret the results. Initially, the study examined whether there were disparities in respondents' experiences of learning AIH consultation among those who conducted AIH consultations in the latest year. As a result, three items ("Consulting with a senior psychiatrist", $P < 0.05$; "Asking for advice from a senior psychiatrist exhibiting the subject's information prior to conducting the consultation", $P < 0.001$; "Asking for comments from a senior psychiatrist and exhibiting them with your report post the AIH consultation", $P < 0.01$) were experienced significantly more often by respondents with experiences of the AIH consultation in the latest years as opposed to those without recent engagements. The results are presented in Table 1.

Table 1 Comparison between designated psychiatrists with recent engagement of administrative involuntary hospitalization consultation and without experience in the experience of ways of learning administrative involuntary hospitalization consultation

		Engaged in AIH consultation in the latest year		*P* value
		Without	With	
Attending seminars held by the government (except mandatory seminars for licensing)	Yes	8	27	NS
	No	118	366	
Attending seminars held by universities, associations, hospitals, *etc*.	Yes	41	137	NS
	No	90	277	
Taught by a supervisor, employer, or senior psychiatrists	Yes	107	365	NS
	No	26	55	
Reading textbook, guidelines, academic papers	Yes	71	233	NS
	No	57	180	
Visiting an AIH consultation of a senior psychiatrist	Yes	84	303	0.037
	No	49	114	
Asking for advice from a senior psychiatrist exhibiting the patient's information prior to conducting the consultation	Yes	42	223	< 0.001
	No	86	189	
Consulting with the other designated psychiatrist in AIH consultation	Yes	57	193	NS
	No	75	216	
Asking for comments from a senior psychiatrist exhibiting them your report post AIH consultation	Yes	28	140	0.006
	No	102	268	
Attending a clinical conference with your case post AIH consultation	Yes	18	70	NS
	No	113	338	
Learning through medical treatment of a case subjected to AIH	Yes	112	341	NS
	No	23	75	

χ^2 test. AIH: Administrative involuntary hospitalization; NS: Not statistically significant.

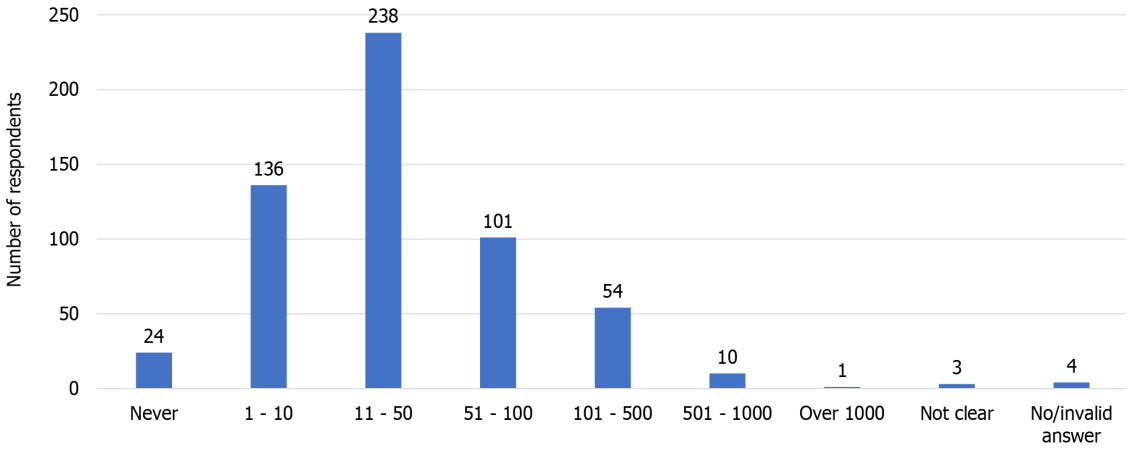

Figure 1 Responses for total personal number of administrative involuntary hospitalization consultations ever performed.

Subsequently, an attempted to compare the disparities in opinions toward each method of learning about AIH consultation between the respondents' specialties. The data of the respondents whose main specialties were general psychiatry and emergency psychiatry were extracted. As a result, three items ("Asking for comments from a senior psychiatrist showing them your report post the AIH consultation", $P = 0.031$; "Attending a clinical conference with your case post the AIH consultation", $P = 0.002$; "Learning through medical treatment of a case subjected to AIH", $P = 0.018$)

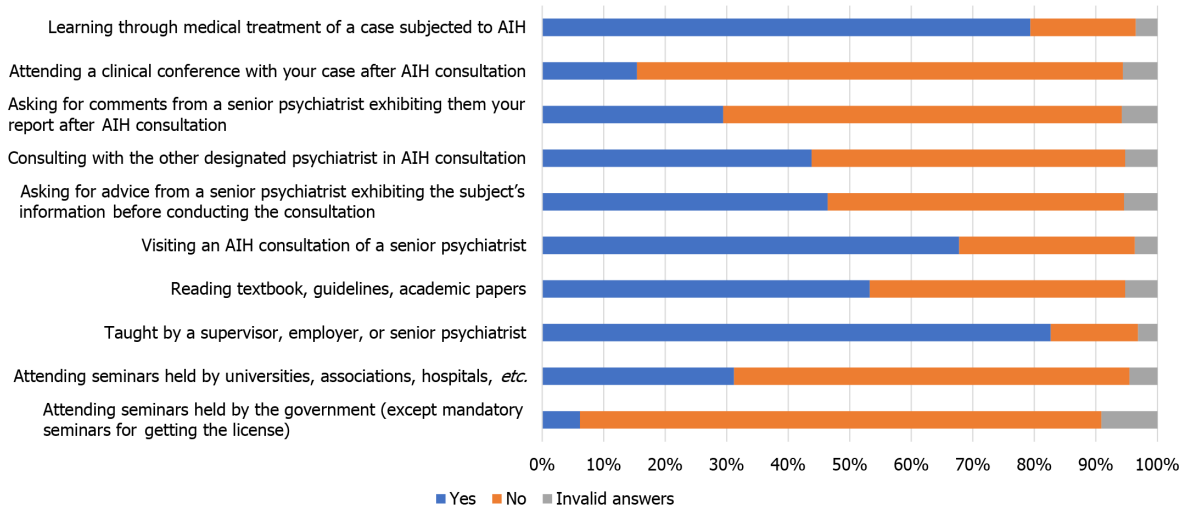

Figure 2 Experience in learning methods for administrative involuntary hospitalization consultation. AIH: Administrative involuntary hospitalization.

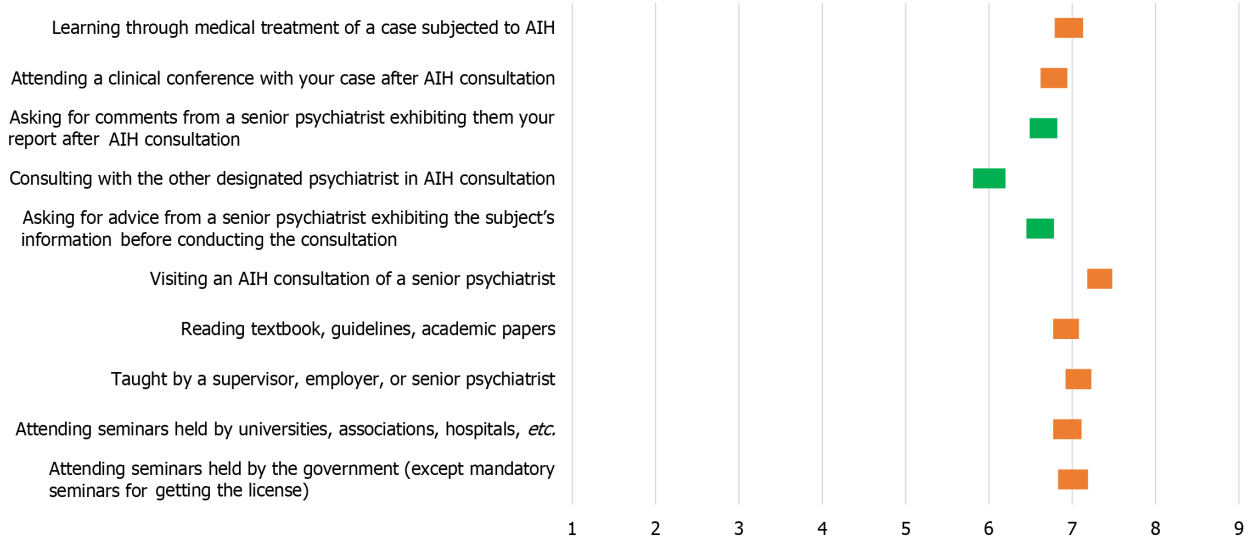

Figure 3 Ideas of optimal methods of learning administrative involuntary hospitalization consultation. Each bar shows 95%CI of the mean score of each item. AIH: Administrative involuntary hospitalization.

were significantly more valued by emergency psychiatrists as opposed to general psychiatrists in terms of learning AIH consultation. The results are presented in Table 2.

DISCUSSION

A questionnaire survey of designated psychiatrists in Japan was conducted to elucidate the current status of AIH consultation education and future needs. As a result, it was revealed that numerous psychiatrists had learned AIH consultation skills through relatively conventional approaches, such as oral education from a supervisor or employer. In addition, most of them emphasized the importance of being involved in the inpatient treatment of hospitalized patients by the governor's order.

Regarding the representativeness of the data obtained in this survey, we should say that the low response rate limits the reliability of the outcome. Nevertheless, the response rate was not remarkably low for an all-inclusive voluntary survey. While the ratio of public to private psychiatric hospitals in Japan is 1:10, the ratio of respondent's belonging was approximately 1:2. Therefore, the present data may be biased toward the opinions of psychiatrists working in the public sector. However, since AIH is deemed as a public work in principle, this bias should not cause significant distortions in the results of the analysis.

As mentioned above, there is no structural training course for forensic psychiatrists offered in Japan. However, it does not mean that psychiatrists who are to deal with offenders with mental disorders undergo no training in Japan. They

Table 2 Comparison between respondents specializing in general psychiatry and emergency psychiatry in their opinions toward methods of learning administrative involuntary hospitalization consultation

Item	Contents	*n*	Mean	SD	Levene's test for variance			Unpaired *t* test		
					F value	*P* value	Variance equality	*t* value	*u*	*P* value
Attending seminars held by the government (except mandatory seminars for licensing)	General	428	6.92	2.180	0.248	0.618	Yes	-1.537	495	NS
	Emergency	69	7.35	2.078						
Attending seminars held by universities, associations, hospitals, *etc*.	General	429	6.85	2.045	0.131	0.718	Yes	-1.576	497	NS
	Emergency	70	7.26	1.886						
Taught by a supervisor, employer, or senior psychiatrist	General	429	7.01	1.912	0.298	0.585	Yes	-1.237	497	NS
	Emergency	70	7.31	1.699						
Reading textbook, guidelines, academic papers	General	428	6.86	1.863	0.539	0.463	Yes	-1.866	496	NS
	Emergency	70	7.30	1.688						
Visiting an AIH consultation of a senior psychiatrist	General	428	7.29	1.884	0.612	0.434	Yes	-1.307	496	NS
	Emergency	70	7.60	1.545						
Asking for advice from a senior psychiatrist exhibiting the subject's information prior to conducting the consultation	General	429	6.56	2.038	0.483	0.487	Yes	-1.437	497	NS
	Emergency	70	6.94	2.091						
Consulting with the other designated psychiatrist in AIH consultation	General	429	6.01	2.277	40.508	0.034	No	-.065	86.831	NS
	Emergency	70	6.03	2.621						
Asking for comments from a senior psychiatrist exhibiting them your report after AIH consultation	General	430	6.51	2.016	0.000	0.992	Yes	-2.163	498	0.031
	Emergency	70	7.07	1.958						
Attending a clinical conference with your case after AIH consultation	General	430	6.63	1.961	10.242	0.266	Yes	-3.167	497	0.002
	Emergency	69	7.42	1.666						
Learning through medical treatment of a case subjected to AIH	General	429	6.85	2.100	0.639	0.424	Yes	-2.380	497	0.018
	Emergency	70	7.49	1.808						

AIH: Administrative involuntary hospitalization; NS: Not statistically significant; *u*: Degrees of freedom.

usually acquire risk assessment and management skills through general psychiatric activities such as inpatient treatment in a psychiatric hospital, and general training programs that are not specialized[10]. Considering that psychiatric evaluation is generally based on the clinician's detailed observation through counseling with the client, a narrative approach for learning assessment skills should be justified. Indeed, designated psychiatrists who have recently been engaged in AIH consultation are more likely to have experienced supervision by senior psychiatrists according to the present study.

Nonetheless, the lack of a standard education protocol for effective assessments in AIH consultations is still a major issue. In this study, most respondents claimed the effectiveness and necessity of official and unofficial seminars as well as learning from textbooks to improve AIH consultation skills. It is broadly believed that forensic fellowships should primarily focus on evaluation and consultations with adequate time, number of patients, and delicate support by a supervisor[11]. In the United States, the primary stream of training of forensic psychiatry was traditionally "on the job" [12]. However, recently, several structured programs for learning forensic psychiatry are established and available for young psychiatrists[13]. In the United Kingdom, training for undergraduate students is also discussed recently, suggesting the challenge of combining theoretical background with teaching practice in this region[14].

The study's findings also suggest that psychiatrists engaging in emergency psychiatry consider the importance of knowing the course of the case post hospitalization for designated psychiatrists. As they are usually involved in treating patients ordered to be hospitalized by the governor, they may occasionally encounter misjudged cases. Ironically, they occasionally learn how to make appropriate decisions through erroneous cases in forensic mental health settings[15].

Sampling bias represents a significant limitation of this study. We distributed the questionnaire to all psychiatric hospitals across Japan. Typically, individuals with a heightened awareness of the subject matter are more inclined to participate in voluntary surveys such as this. Consequently, there is a potential for the current results to overrepresent responses from individuals possessing expertise or in-depth understanding of forensic psychiatric education. In essence, the average psychiatrist may not perceive the need for it to the same extent as indicated by the results. Addressing this issue and promoting its significance among general psychiatrists pose additional challenges.

CONCLUSION

A questionnaire survey was conducted to investigate the learning methods utilized for AIH consultations. The study's findings indicate that many psychiatrists have not undergone structured training specifically tailored for AIH consultations. Instead, narrative approaches with oral teaching remain prevalent in clinical practice among designated psychiatrists. The establishment of a standardized protocol for AIH consultations is urgently needed. Additionally, incorporating feedback from the inpatient treatment section for psychiatrists who have conducted AIH consultations is crucial for enhancing their precise assessment skills. The researchers advocate for the establishment of a comprehensive program package in forensic mental health without delay. Such a program should encompass training in risk assessment skills, opportunities for specialist fellowships involving accompanying consultations with offenders with mental disorders, and collaboration with clinicians working in emergency psychiatric units. The researchers are committed to undertaking further research to develop this program further. Ultimately, it is anticipated that these new programs will be integrated into an official training course administered by the government.

FOOTNOTES

Author contributions: Shiina A, Niitsu T, and Fujii C designed the research study; Shiina A, Niitsu T, and Iyo M performed the research; Shiina A analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Prospective Study

Effects of strengthening prospective nursing practice on sleep quality, anxiety, and depression of awake patients in intensive care unit

Fei Lin, Lei Liu

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Abstract

BACKGROUND

The intensive care unit (ICU) is a specialized hospital department. Awake patients in the ICU frequently encounter adverse psychological states, such as anxiety and fear, often accompanied by poor sleep quality. This situation has garnered significant attention within the medical community.

AIM

To investigate the impact of prospective nursing intervention strategies on the sleep quality and negative emotional state of conscious ICU patients.

METHODS

One hundred and twenty ICU awake patients admitted to our hospital were selected and randomly divided into control (n = 60) and observation (n = 60) groups. Patients in the control group were cared for using the conventional nursing model, while patients in the observation group were cared for using the prospective nursing model. Sleep improvement was assessed using the International Standardized Sleep Efficiency Formula and Pittsburgh Sleep Quality Index (PSQI). The PSQI, Generalized Anxiety Disorder 7-item (GAD-7) scale, Self-Depression Scale (SDS), and satisfaction before and after treatment were used to assess the negative emotional states of patients under the two care models.

RESULTS

Patient satisfaction in the observation group was significantly higher than in the control group. The GAD-7 and SDS scores in the observation group were significantly lower than those in the control group, and the total effective rate of sleep improvement in the observation group was significantly higher than in the control group. After treatment, the PSQI scores of the two groups significantly decreased (P < 0.05). The decrease in the observation group was more significant

than that in the control group, and the difference between the two groups was statistically significant.

CONCLUSION
Prospective nursing interventions can improve sleep quality and psychological levels and significantly affect conscious patients in the ICU, which is worthy of clinical application.

Key Words: Prospective nursing; Intensive care unit; Sobriety; Mental health sleep quality; Anxiety and depression

Core Tip: This study establishes a theoretical foundation for the practical application of prospective nursing methods in clinical care and the rehabilitation prognosis of conscious patients within the intensive care unit (ICU). In the future, more attention should be focused on the sleep quality and mental well-being of awake patients in the ICU.

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INTRODUCTION

Recent medical advances have increased the number of critically ill survivors in intensive care units (ICUs)[1]. Several studies have evaluated the prognosis of ICU-conscious patients[2]. Awake patients in the ICU often face complex rehabilitation processes, including long-term physical and cognitive impairments and poor quality of life[3,4]. The ICU constitutes a specialized department within the hospital. Conscious patients frequently experience negative psychological emotions, such as anxiety and fear, while those in ICUs often report poor sleep quality[5]. Their sleep patterns are highly dispersed and lack deep restorative rapid eye movement sleep. In the ICU environment, various factors are thought to lead to sleep deprivation, such as underlying disease status, pain, stress, anxiety, exposure to noise and irregular light, laboratory sampling, and mechanical ventilation[6,7]. Simultaneously, patients within the ICU often have varying degrees of depression, anxiety, and other adverse symptoms, which will destroy the physiological balance of patients and aggravate the symptoms. The mental symptoms of ICU-conscious patients were mainly related to the decline in their quality of life[4,8,9]. Recently, people have become increasingly interested in the mental health outcomes of ICU patients [10]. Recent systematic reviews focus on different aspects of mental health in this population, such as post-traumatic stress disorder and depression[5,9]. However, to the best of our knowledge, there are no published systematic reviews on nonspecific anxiety symptoms and sleep quality in awake patients in the ICU. Therefore, we decided to use a prospective nursing model to increase information exchange, psychological care, and sleep care, specifically for awake patients in the ICU, and to evaluate the effect of this nursing model using the Pittsburgh Sleep Quality Index (PSQI), Generalized Anxiety Disorder 7-item (GAD-7) scale, and Self-Depression Scale (SDS). Our goals were to: (1) Examine the prevalence of anxiety symptoms in awake ICU patients; (2) Evaluate sleep quality symptoms in awake ICU patients; (3) Determine patients' risk factors during ICU admission; and (4) Evaluate intervention measures to prevent or treat anxiety symptoms after ICU admission. Prospective nursing, considering factors that could contribute to patients' negative moods and sleep disturbances, aims to mitigate these issues and improve mood and sleep quality for patients.

MATERIALS AND METHODS

Research designers and participants

This was a controlled study; the participants were conscious patients admitted to our hospital's ICU. Nursing interventions and questionnaire surveys were administered to the two research groups through randomized grouping. The inclusion criteria of the subjects were as follows: (1) The age of the subjects was more than 18 years old; (2) The patients were conscious; (3) All patients were admitted to ICU in our hospital; (4) All patients signed informed consent before participating in the study; and (5) Good compliance and ability to complete all questionnaires. Patients with severe heart, lung, liver, and renal diseases; cognitive impairment; and inability to complete the nursing research were excluded from the study (Ethical Approval Number: 231005).

Investigation methods

The control group included nursing and drug interventions. The patient's vital signs were closely monitored, and routine nursing care in the ICU was provided. Observation group: The prospective nursing model was implemented to provide care for the patients in the observation group. The instruments used in this study had a certain degree of accuracy and

stability and the consistency of multiple measurements was good under the same conditions.

The primary measures included: (1) Information transmission: Upon confirming the patient's conscious state, the basic environment, attending doctor, and competent nurse were introduced to the patient to instill a sense of security. Detailed explanations of the treatment and nursing measures were provided, emphasizing their necessity; and (2) Communication strategies: For patients who faced difficulties in verbal expression, active communication was established using hand gestures or communication *via* pen and paper. This approach aimed to ensure patients correctly understood their condition upon awakening. Additionally, dedicated caregivers were assigned to provide bedside care for patients experiencing movement disorders in their hands, feet, or heads. These caregivers conveyed thoughts and intentions by interpreting eye-opening or closing movements, shaping lips, and other non-verbal cues. Psychological nursing: Nurses should care about patients as much as possible, communicate with them effectively, strengthen ward inspections, and pay attention to nonverbal communication to convey encouragement and comfort to patients. The degree of pain was evaluated based on the patient's facial expressions. Patients who express themselves in words should listen patiently to their complaints, and their reasonable requirements should be satisfied as much as possible. Sleep care: Fully understand the sleep status of each patient and try to create a clean and quiet environment. Music can be played when individuals sleep; night equipment alarms should be set in an appropriate range; treatment and nursing-related operations should be concentrated during the day as far as possible; and movement, walking, talking, and closing the door should be performed gently to avoid waking the patient. Paying attention to the cleanliness and quietness of the environment: Patients can play their favorite music, but the volume must be adjusted between 25-30 dB. At night, lights must be turned off; floor lights must be turned on for easy inspection. Nursing operations can be arranged when the patient is awake, with gentle movements to prevent them from being interrupted during sleep and the inability to fall asleep. Early exercise guidance for patients: After thoroughly analyzing the recovery of the disease for walkable patients, assist in walking exercises at a designated time, with a distance of 500-1000 m and a time limit of 20 min. Attention should be paid to monitoring the various signs during exercise to determine tolerance. Once symptoms, such as palpitations and shortness of breath, occur, they stop immediately.

General information questionnaire

General information about the participants was collected, including name, age, sex, place of residence, marital status, income, and previous prevalence of chronic diseases.

PSQI

The PSQI was used to evaluate the participants' sleep quality in the past month. It comprises 19 self-assessment items and five other self-assessment items, of which the 19th self-assessment project and five other self-assessment items do not participate in the score; here, only 18 self-assessment items are involved[11]. A total of 18 items comprised seven components; each component was scored according to a grade of 0-3, the cumulative score for each element was the total score of the PSQI, and the total score ranged from 0-21. Higher scores indicate worse sleep quality. Score 0-5: Normal sleep quality; 6-10: Mild sleep disorder; 11-15: Moderate sleep disorder; 16-20: Severe sleep disorder; 21: Very severe sleep disorder.

Generalized Anxiety Scale

The GAD-7 had seven entries. Each entry is divided into four levels: 3 = almost every day, 2 = more than a week, 1 = several days, 0 = not at all. The total score is the sum of the scores of the seven entries, and the total score ranges from 0-21 points. Furthermore, 0-4 points were no clinically significant anxiety, 5-9 points, mild anxiety: 10-14 points, moderate anxiety: 2-15 points, or severe anxiety[12].

SDS

The SDS was developed by Zung in 1965. The scale comprises 20 items that reflect subjective feelings of depression, each of which is divided into four grades according to the frequency of symptoms, of which 10 are positive and 10 are negative. Individual scores for the 20 items were added to obtain an approximate score. The coarse score is multiplied by 1.25 and rounded to the nearest integer to obtain the standard score. The upper limit of the normal reference score was 53. Additionally, 53-62 years are considered to have mild depression, 63-72 years are believed to have moderate depression, and those aged 72 years or older are considered to have severe depression[13].

Evaluation of patient satisfaction

Satisfaction evaluation method: On the day the patient was discharged from the hospital, nursing service satisfaction during the treatment was scored anonymously, with 100 points as the full score, more than 80 points as satisfaction, less than 60 points as dissatisfaction, and the rest as basic satisfaction.

Statistical analysis

The SPSS Windows software version 26.0 was used to analyze the data. Continuous data were normally distributed and expressed as means and percentages. The median (quartile) was used to describe continuous variables with skewed distributions, and classified variables were expressed as numbers and percentages (%). A *t*-test was used to analyze the differences between the two groups of quantitative data. The χ^2 test was used to analyze multiple groups of data. Logical regression was used to analyze risk factors. All the analyses were conducted at the test level of $\alpha = 0.05$, and the difference was considered statistically significant when $P < 0.05$.

RESULTS

General information about the study population

Between January 2022 and August 2023, 120 conscious patients at our hospital were randomly divided into control (n = 60) and observation (n = 60) groups. In the control group, there were 37 male and 23 female patients. The patients were admitted to the ICU for 1-6 d. The average treatment time was 2.7 ± 0.6 d, the patients were 20-73 years old, and the average age was 42.3 ± 6.4 years old. Additionally, 33 male and 27 female patients were in the observation group. The hospitalization time of the patients was 1-6 d. The average treatment time was 2.4 ± 0.5 d, the patients were 19-75 years old, and the average age was 43.9 ± 5.2 years old. There were no significant differences in the abovementioned indices between the observation and control groups (P > 0.05; Table 1).

Analysis of sleep and psychological state of the two groups of participants

Analysis of the difference in sleep quality between the two groups: The sleep analysis among the two groups revealed that six patients in the observation group had poor sleep quality, thus accounting for 10.0%. In comparison, the control group was 25, accounting for 41.7%. These differences were statistically significant (P < 0.05; Table 2).

Analysis of GAD-7 scale differences between the two groups: To evaluate the anxiety state of the two groups, the anxiety state of the control group was significantly higher than that of the observation group (P < 0.001). The patients' average scores were 3.9 in the observation group and 10.2 in the control group (Table 3).

Analysis of the difference in depressive status between the two groups: The depression state in the case group was significantly higher than that in the control group (P < 0.05). Depression rates were 66.5% and 86.0% in the case and control groups, respectively (Table 4).

Effects of disease knowledge and satisfaction compared between the two groups

In the observation group, there were 58 satisfied patients, resulting in a satisfaction rate of 96.67% and an awareness rate of 91.67%. Conversely, the control group had 45 satisfied patients, equating to a satisfaction rate of 75.00% and an awareness rate of 70.00%. The observation group exhibited significantly higher rates than the control group, with a statistically significant difference (P < 0.05). The results are presented in Tables 5 and 6.

DISCUSSION

Patients typically face severe conditions, leading to psychological distress marked by frequent fluctuations, and experience fear, depression, and other negative emotions. These factors contribute to poor sleep quality and can significantly impact the prognosis[10]. Therefore, it is necessary to provide humanized nursing intervention measures to improve the quality of sleep and life and reduce the psychological burden on patients. Addressing the importance of sleep and comfort during hospitalization in critically ill patients has been highlighted as a priority in intensive care. This study adopted prospective nursing care, including health education, teaching relevant health knowledge to sober patients in the ICU, eliminating fear, actively cooperating with treatment, explaining disease mechanisms, and improving treatment enthusiasm. Psychological nursing is characterized by individualization, integration, and effectiveness. This can maintain patients psychological and physiological balance and enhance their compliance with treatment to further improve the curative effect, reduce complications, and improve prognosis actively understanding patients negative mood, dredging psychological problems, informing patients about the impact of positive treatment, enhancing treatment confidence, listening to patients worries, providing answers, and eliminating destructive emotions furthermore, completing treatment with optimistic, positive, and healthy attitudes. Maintaining comfort in the treatment environment, creating a warm environment, reducing noise as much as possible improving sleep quality, ensuring adequate sleep caring for patients, communicating with patients, encouraging patients to express their emotions, eliminating strangeness, and enhancing their self-esteem. In the nursing process, patients can effectively reduce their panic about entering an unfamiliar environment by taking the initiative to introduce the environment. Inform the patient of the positive aspects of the results and the positive aspects of the recovery. The results indicated that after treatment, the PSQI score of the observation group decreased compared to the control group. Moreover, patient satisfaction in the observation group significantly surpassed that in the control group. Additionally, the GAD-7 and SDS scores among patients receiving prospective nursing intervention in the observation group were notably lower than those in the control group. Furthermore, the overall effective rate of sleep improvement was higher in the observation group than in the control group. Simultaneously, early exercise intervention can help some patients recover their physical function as soon as possible and promote blood circulation positively affecting the recovery from diseases. All the processes of nursing staff in the entire nursing process take into account the actual condition of patients and realize patient-centered nursing. This has a positive effect on nursing satisfaction. Both the physical and psychological aspects of awake patients are affected to a certain extent, and it is relatively complex to perform nursing interventions. To improve the quality of care for awake patients, nurses should possess proficient nursing skills, extensive clinical experience in the ICU, and the capability to address various challenges encountered during actual caregiving. In prospective nursing interventions, the psychological level of patients is always emphasized. By reinforcing health education and providing psychological counseling to ICU patients, we can strive to fulfill their physical and mental needs to the fullest extent possible. This approach can enhance their emotional well-being, promote treatment compliance, shorten the gap between nurses and patients, and foster a

Table 1 General survey of the case and control groups

Variable		Observation group (*n* = 60)	Control group (*n* = 60)	*P* value
Year		43.9 ± 5.2	42.3 ± 6.4	0.091
Sex	Male	33	37	0.459
	Female	27	23	
Current address	Urban	16	7	0.037
	Townships	44	53	
Education	Junior high school and below	34	42	0.314
	High school	11	8	
	College and above	15	10	
Economic	≤ 2000	6	7	0.176
	2001–2999	23	32	
	≥ 3000	31	21	
Smoke	Yes	36	29	0.200
	No	24	31	
Drink	Yes	45	50	0.261
	No	15	10	
Inheritance	Yes	22	6	< 0.001
	No	38	54	
Married	Yes	51	47	0.345
	No	9	13	

Table 2 Analysis of the difference in sleep quality between the two groups, *n* (%)

Groups	Good quality of sleep	Poor sleep quality	Total
Observation group	54 (90.0)	6 (10.0)	60
Control group	35 (58.3)	25 (41.7)	60
χ^2			15.7
P value			< 0.001

Table 3 Analysis of the anxiety status of the two groups of patients

Groups	Anxiety level score	Total
Observation group	3.9 ± 1.2	60
Control group	10.2 ± 3.2	60
t		8.21
P value		< 0.001

positive nurse patient relationship. The prospective nursing service model is a type of preventive nursing. By setting the research objects and methods in advance, we can further standardize nursing service behaviors, raise related questions predictably, and improve service homogeneity. Thus, we can provide scientific and effective forward-looking nursing service measures for patients, reduce nursing errors, and avoid the risks posed by nursing services to the greatest extent possible. Owing to the limited sample size of this study, larger multicenter randomized controlled studies are needed to expand our findings.

Table 4 Analysis of depression in the two groups of patients

Groups	Standard score	Total
Observation group	38 ± 7.4	60
Control group	61 ± 9.2	60
t		19.2
P value		< 0.001

Table 5 Condition awareness table

Groups	Number of examples	Knowledge of illness		
		Totally aware	Aware	Not sure
Observation group	60	55	3	2
Control group	60	42	8	10
χ^2				19.2
P value				< 0.001

Table 6 Nursing job satisfaction table

Groups	Number of examples	Satisfaction with nursing work		
		Totally satisfied	Basically satisfied	Not satisfied
Observation group	60	58	2	0
Control group	60	45	11	4
χ^2				8.31
P value				< 0.001

CONCLUSION

This study established that compared to the control group, the observation group with the prospective nursing intervention was less likely to have decreased sleep quality, anxiety, and depression. Additionally, they experienced significantly improved conditions, awareness, and discharge satisfaction. The study establishes a theoretical foundation for clinical nursing and rehabilitation prognosis of conscious patients within the ICU. In summary, the use of prospective nursing interventions in treating this disease has achieved a good clinical effect and is worthy of clinical application.

FOOTNOTES

Author contributions: Lin F and Liu L contributed equally to this work. Lin F and Liu L contributed to designed the research study, performed the research, contributed new reagents and analytical tools, and analyzed the data and wrote the manuscript; and all authors have read and approved the final manuscript.

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SCIENTOMETRICS

Explosion of research on psychopathology and social media use after COVID-19: A scientometric study

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Abstract

BACKGROUND

Despite advances in research on psychopathology and social media use, no comprehensive review has examined published papers on this type of research and considered how it was affected by the coronavirus disease 2019 (COVID-19) outbreak.

AIM

To explore the status of research on psychopathology and social media use before and after the COVID-19 outbreak.

METHODS

We used Bibliometrix (an R software package) to conduct a scientometric analysis of 4588 relevant studies drawn from the Web of Science Core Collection, PubMed, and Scopus databases.

RESULTS

Such research output was scarce before COVID-19, but exploded after the pandemic with the publication of a number of high-impact articles. Key authors and institutions, located primarily in developed countries, maintained their core

positions, largely uninfluenced by COVID-19; however, research production and collaboration in developing countries increased significantly after COVID-19. Through the analysis of keywords, we identified commonly used methods in this field, together with specific populations, psychopathological conditions, and clinical treatments. Researchers have devoted increasing attention to gender differences in psychopathological states and linked COVID-19 strongly to depression, with depression detection becoming a new trend. Developments in research on psychopathology and social media use are unbalanced and uncoordinated across countries/regions, and more in-depth clinical studies should be conducted in the future.

CONCLUSION

After COVID-19, there was an increased level of concern about mental health issues and a changing emphasis on social media use and the impact of public health emergencies.

Key Words: Psychopathology; Social media; Bibliometrics; Web of Science; PubMed; Scopus

Core Tip: Rapid changes in the social health environment and the media have seriously affected human mental health. It is therefore important to capture research topics and trends in psychopathology and social media before and after the coronavirus disease 2019 (COVID-19) epidemic through bibliometrics. The study, which examined 4588 publications from the Web of Science, PubMed, and Scopus databases, identified an explosion in the number of findings after the COVID-19 outbreak, whereas such studies had been rare before the pandemic. As researchers increasingly focus on gender differences in psychopathological states and identify strong links between COVID-19 and depression, the detection of depression will become a new trend in the field of psychopathology and social media use.

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INTRODUCTION

Psychopathology is the study of the occurrence, development, and treatment of mental illnesses. Due to intensified social competition and information overload, psychological stress factors in modern societies have increased significantly, and looser social connections have made people feel alienated. In this context, mental illness is becoming a prominent social problem worldwide. According to United States Census Bureau data, three times as many adults in the United States experienced depression or anxiety in April to May 2020 than in the early stages of coronavirus disease 2019 (COVID-19) in 2019[1].

Social media refers to interactive platforms based on mobile communication and internet technology. Essentially, social media platforms allow people to create and exchange user-generated content. People search for information, record their lives, express their opinions, and share their emotions on social media platforms, which have become extremely popular due to the development of internet technology. In addition, the use of social media increased significantly due to the social isolation imposed during COVID-19[2]. Many individuals with mental disorders seek help through social media platforms, and social media is increasingly integrated into the professional lives of researchers, transforming many fields of study. Through social media, researchers, including psychopathologists, can conduct peer communication, publicise and communicate professional knowledge to patients in new ways, and employ the abundant information available on social media platforms to identify the opinions, attitudes, and emotions of internet users and detect and intervene in psychological crises[3]. However, the speed and comprehensive coverage of social media can lead to the spread of misinformation. Fake news and conspiracy theories may mislead the public, causing a biased understanding of the pandemic and triggering social panic and chaos. Moreover, the excessive use of social media can cause mental illnesses, such as internet addiction, social anxiety, and negative emotions, such as loneliness and depression[4]. In addition, social media may cause additional harm to people who already have mental illnesses, affecting the treatment of their conditions [5]. Therefore, research on psychopathology and social media holds vital social and academic value.

There have been many valuable achievements in the psychopathology and social media fields. For example, scholars have measured the symptomatologic features of social media overuse, based on the criteria for substance and behavioural addiction provided by the Diagnostic and Statistical Manual of Mental Disorders[6]. Other scholars have discussed the multi-modal hierarchical attention model of depression detection for social media use[7,8]. However, these achievements have been relatively fragmented. Due to rapid changes in the media environment and social norms, it is vital to identify hot research topics and trends in psychopathology and social media *via* bibliometrics. Bibliometrics - also known as scientometrics - uses mathematical and statistical methods to analyse the elements of academic papers, such as journals, authors, countries, and institutions, to analyse the frequencies and relationships of keywords, and to identify research

frontiers and trends in specific fields. Bibliometrics has developed rapidly in recent years. Some scholars have used bibliometrics to explore medical studies on pseudo-information (or misinformation) in social media[9], while others have discussed the bibliometrics of parasitology studies on social media[10]. However, no bibliometric analysis has considered the relationship between psychopathology and social media use. To fill this gap, we analysed relevant English-language literature in the Web of Science Core Collection (WOSCC), PubMed, and Scopus databases to systematically examine current research status and provide valuable references for future researchers investigating psychopathology and social media use. We devoted particular attention to changes in this research field before and after the outbreak of COVID-19, which may provide a reference for researchers considering psychopathology and social media use when future health emergencies arise.

MATERIALS AND METHODS

Data source and retrieval strategy

We selected three English-language databases - WOSCC, PubMed, and Scopus - as sources of data up to March 2023 and extracted relevant literature according to the following search formula based on the full texts of articles: ("psychopathology" OR "pathological OR psychology" OR "psychotherapy" OR "anxiety disorders" OR "depression" OR "schizophrenia" OR "phenomenology" OR "Freud" OR "emotional disorders" OR "trait anxiety" OR "perfectionism" OR "Jaspers" OR "psychosis " OR "mental disorder") AND ("Weibo" OR "*microblog*" OR "Tencent" OR "Soho" OR "Netease" OR "Twitter" OR "social media" OR "Facebook"). To ensure the accuracy of the results, we based the selection of literature on the double-blind principle, while the title and abstract of each source were separately and manually screened by Zhang MD and He RQ. We excluded duplicate sources and non-academic literature, such as news and newsletters, as well as literature unrelated to the topic and non-English-language literature. If the screening results of the two practitioners did not correspond, Chen G made the final decision regarding inclusion in the study. Finally, the data for this study were provided by 4588 publications (Figure 1). We exported the relevant information (*e.g.*, title, author, keywords, organization, *etc.*) from each paper into BibTeX format for further analysis.

Bibliometric method

We used Bibliometrix to obtain relevant statistics for this study. This is a commonly used open-source bibliometric toolkit developed by Aria and Cuccurullo, based on the R platform. The statistical analysis of the element and quantitative characteristics of the literature enabled us to directly and flexibly describe the status and development trends of research on psychopathology and social media use[11-14]. We employed Bibliometrix to display the volume of publications; analyse the impact of journals and authors, demonstrate how institutions, countries, and authors collaborated in the studies, evaluate the core papers, and analyse keyword characteristics.

Analysis of the influence of authors and journals

We used the *h*-index, *g*-index, *m*-index, and total citation (TC) and impact factor (IF) indices to determine the influence of authors and journals. The *h*-index indicates the number of times a scholar's paper has been cited by other scholars. The *g*-index ranks papers from the highest to the lowest numbers of citations and determines whether the total number of citations of the first *g* papers is greater than or equal to g^2. The *g*-index combines the *h* and TC indices for each paper, which can prevent certain papers with strong academic influence from being missed. The *m*-index is calculated according to the following formula: *h*-index for authors/number of years since the first publication. The *m*-index enables authors with different career lengths to be compared[15].

We conducted a collaboration network analysis by identifying the authors, institutions, and countries that appeared in the same papers. In a collaboration network, the larger the node, the more frequently the element appears in the network, and the thickness of the connection line represents the intensity of cooperation. For example, if a paper has two or more authors, there will be a link between these authors in the collaboration network. Different colours in the network represent diverse research groups or communities.

After the core papers on psychopathology and social media use were evaluated, we introduced TCs as a factor. The number of times other researchers had cited a paper indicated the potentially higher quality and value of the paper. Papers with high TCs are likely to stimulate new ideas and directions of research cooperation, and they may play an important role in promoting scientific research innovation or providing basic knowledge of certain research fields.

Research hotspot analysis

Relevant analysis based on keywords is the most important element of bibliometric research, and it enabled us to identify hot research topics in the fields of psychopathology and social media use. We conducted an analysis of the hot research topics by combining keyword co-occurrence and co-word analyses.

Keyword co-occurrence indicates the occurrence of two or more keywords in a paper, and co-occurrence analysis can directly demonstrate the correlations between keywords. The size of a node in a co-occurrence plot is proportional to the frequency of its occurrence in the retrieved articles, reflecting the centrality of keywords, and the thickness of the lines between nodes reflects the intensity of keyword associations. Keywords of the same colour belong to a cluster, thus enabling the meaning sets of the interrelated words to be determined by colour.

In a thematic map, the horizontal axis indicates the degree of keywords' convergence to the centre, while the vertical axis presents the relative densities of keywords. By dividing the axes into four quadrants, the dynamic development of

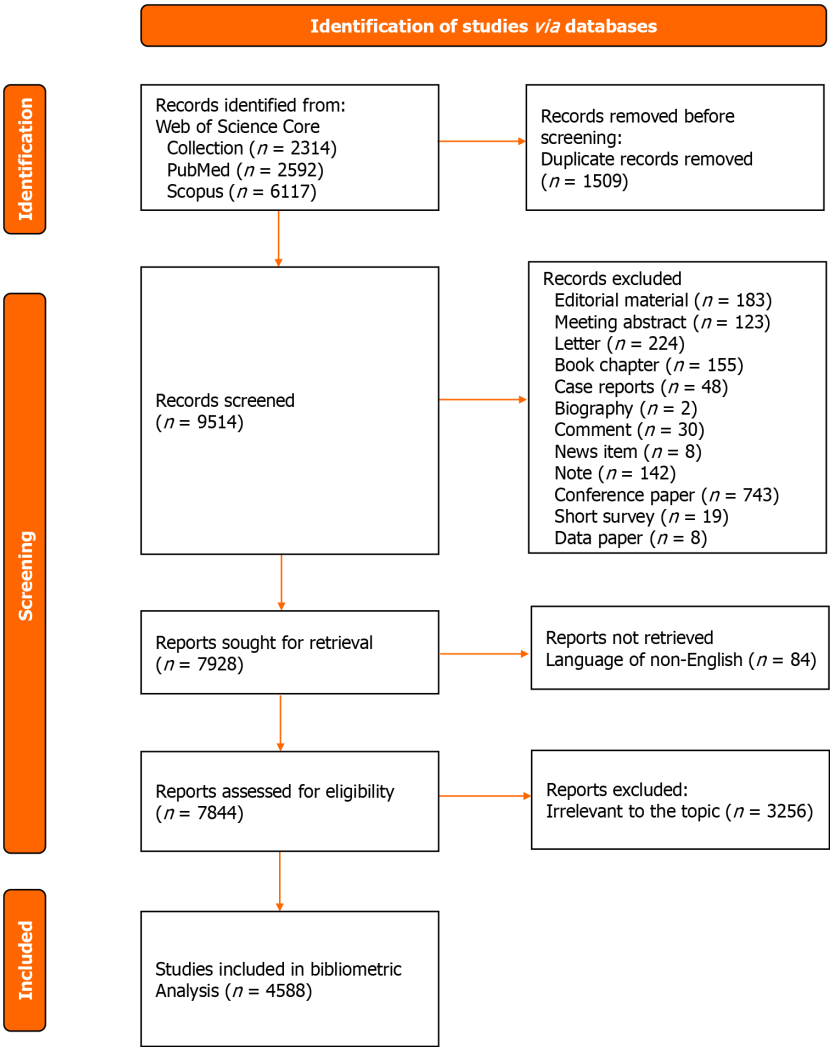

Figure 1 PRISMA flowchart of the data analysis for the current study.

the research can be displayed more intuitively. Motor themes (the themes that are fully developed and have high research value) with high centrality and density are distributed in the top-right quadrant, representing key research areas. Niche themes are distributed in the top-left quadrant and are less strongly related to other themes, but because of their high density, they may be related to other themes over time and become motor themes. The bottom-left quadrant includes emerging or declining themes with low density and low centrality, suggesting that in the field of research, these are emerging topics or topics that are disappearing. The bottom-right quadrant contains the basic themes, which have high centrality but low density. These themes are vitally significant, but not yet fully developed, indicating possible future research trends. In a trend topic map, the line segment represents the high frequency of keywords appearing during a specified period, and the circle size represents the frequency of the occurrence of emerging keywords.

RESULTS

Publication distribution

The number of publications in different years reflected the development stages of research in this field (Figure 2). The first stage constituted the years prior to 2015, and the number of relevant papers in this stage was relatively small. The second stage was from 2015 to 2019, when there was a small increase in the number of publications. The third stage was from 2019 to date. The number of relevant published papers increased dramatically following the outbreak of COVID-19, reaching a peak of 1173 publications in 2022. Due to time constraints in relation to data collection, the number of publications listed in 2023 did not reflect the total output for this year. In general, the output of the research on psychopathology and social media use demonstrated annual increases and an explosive increase after the COVID-19 pandemic.

Figure 3 presents the numerical rankings of the papers published by different countries, journals, institutions, and authors. The overall situation and the situations before and after the COVID-19 outbreak are presented in Figure 3A-C, respectively. In terms of journals, the *Journal of Medical Internet Research* published the most papers (193 papers, 4.2%), followed by the *International Journal of Environmental Research and Public Health* (175 papers, 3.8%), and *BMJ OPEN* (138

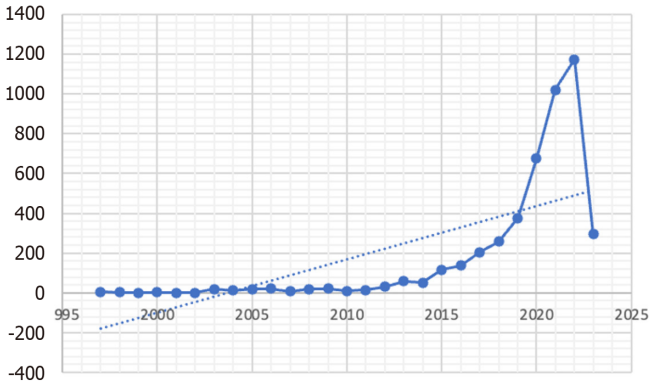

Figure 2 Global scientific research on psychopathology and social media use.

papers, 3%). The top 10 journals collectively published more than one-fifth of the total number of papers, and most of the listed journals were located in the Journal Citation Reports edition 2023 (JCR) ranking quartiles I or II. Regarding institutions, high-yielding institutions were located in North America, Europe, and Oceania. A few high-yielding institutions were located in Asia, such as China (Sun Yat-Sen University) and Bangladesh (Jahangirnagar University). Four of the top 10 high-yielding institutions were located in the United States. Regarding authors, Haro JM *et al*. published the most papers (72 papers), followed by Novick D (64 papers), and Griffiths MD (53 papers). From the perspective of countries, the countries with the highest number of publications were the United States, China, and Australia. A comparison of the publication output before and after COVID-19 revealed that the COVID-19 outbreak played an important role in the yield of scientific research on psychopathology and social media use. The number of studies in China and India significantly increased after COVID-19 due to the high incidence and widespread impact of the pandemic in these countries. In addition, the categories of high-yielding journals also varied; prior to COVID-19, medical and cybertechnical journals were plentiful, but after the pandemic, the number of environmental and social science journals increased significantly.

Impacts of journals and authors

The results for the *h*, *g*, *m*, TC, and IF indices are presented in Tables 1 and 2. According to the *h*-index, the most influential author was Haro JM. According to the *h* and TC indices, the most influential author was Griffiths MD. According to the *m*-index, the most influential author was Escobar-Viera CG.

Among the high-impact journals covering research on psychopathology and social media use, the *Journal of Medical Internet Research* had the highest *h*-index (31), indicating that of the 31 papers with the top TCs in this journal, each paper had been cited at least 31 times. The second- and third-ranked journals according to the *h*-index were *Computers in Human Behavior* (25) and *Plos One* (24). According to the *m*-index, the above three journals were also the top three. In terms of the *g* and TC indices, *Plos One* was the most influential journal in this field. The journal with the highest IF for research on psychopathology and social media was Computers in Human Behavior (8957).

Analysis of research collaboration

The overall collaboration network is presented in Figure 4. In terms of national collaboration (Figure 4A), there were three groups: A United States-led group (green), including developed countries such as Australia, the United Kingdom, and Canada; a China-led group (red), which included China, Saudi Arabia, India, South Korea, and other Asian countries; and a European group (blue), consisting of countries such as Spain, Germany, Poland, and Denmark. In this national collaboration network, the United States had the largest node and the most complex links with other countries, holding the global core position in research on psychopathology and social media use.

In terms of institutional collaboration (Figure 4B), there were clear collaboration networks between neighbouring institutions, especially regarding intercountry collaboration. For example, the University of California, the University of Pittsburgh, the University of Washington, the University of Michigan, and other United States institutions formed relatively strong collaboration networks. International collaboration was dominated by institutions in developed countries, which occupied larger areas and had larger nodes in the collaboration network.

An analysis of author collaboration revealed different colours of collaboration networks (Figure 4C), and we observed the formation of an independent network consisting of high-yielding teams, including researchers such as Haro JM and Novick D, who worked closely together.

Next, we evaluated the differences in collaboration networks before and after COVID-19. After COVID-19, the number of institutions and authors in the network increased significantly, and the network structure became more complex. Moreover, international collaboration became more evident after COVID-19. While Lebanon and South Africa had no collaboration with the other countries before COVID-19 (Figure 5A), they collaborated extensively with other countries after the pandemic (Figure 6A). The United States maintained its core position, uninfluenced by COVID-19 (Figures 5A and 6A). Institutional collaboration in the pre-COVID-19 period was concentrated primarily in developed countries; however, collaboration after COVID-19 revealed an increased involvement of institutions in developing countries, such as

Table 1 The top ten most impactive authors

Author	*H*_index	*G*_index	*M*_index	TC	PY_start
Haro JM	22	42	1.048	1804	2003
Griffiths MD	19	45		2107	
Novick D	19	37	0.905	1414	2003
Suarez D	14	31	0.737	988	2005
Lin CY	12	27	2	780	2018
Primack BA	12	24	1.5	1842	2016
Shensa A	11	23	1.375	1811	2016
Sidani JE	11	21	1.375	1809	2016
Brailovskaia J	10	22	1.25	490	2016
Escobar-Viera CG	10	25	1.429	997	2017

TC: Total citation.

Table 2 The top ten most impactive journals

Journals	*H*_index	*G*_index	*M*_index	TC	IF
Journal of Medical Internet Research	31	52	2.818	3063	7.076
Computers in Human Behavior	25	53	2.273	3174	8.957
Plos One	24	62	2.182	3864	3.752
Journal of Affective Disorders	17	58	1.545	3440	6.533
Cyberpsychology, Behavior, and Social Networking	16	27	1.455	1234	6.135
Frontiers in Psychiatry	16	31	1.778	1042	5.435
International Journal of Environmental Research and Public Health	15	43	1.5	1970	4.614
BMJ Open	13	26	1.444	749	3.006
JMIR Mental Health	13	34	1.444	1168	6.332
Psychiatry Research	12	34	0.706	1179	2.493

TC: Total citation; IF: Impact factor.

Jahangirnagar University in Bangladesh and the University of Hong Kong and Hong Kong Polytechnic University in China (Figures 5B and 6B). A number of new scholars and research groups also emerged after COVID-19, including Griffiths MD, Pakpour AH, and Lin CY (Figures 5C and 6C).

Details of the core papers

The top 10 cited papers are presented in Table 3. Regarding time, although psychopathology and social media use had been studied since the end of the twentieth century, the top 10 cited papers were published after 2010, and 4 of them were published after the COVID-19 outbreak. Regarding research methods, traditional meta-analyses (papers 1 and 5)[16,17], cross-sectional studies (papers 2 and 9)[18,19], and experimental study (paper 2)[19] were used in these most frequently cited papers to explore correlations between social media use and negative psychological states. A small number of studies also used online ecological recognition based on machine-learning predictive models (paper 7)[20] and other advanced methods. The research subjects focused primarily on COVID-19 (papers 1, 4, 5, and 7)[16,17,20,21] and adolescents (papers 3 and 10)[22,23] , which reflected hot research topics in this field. The most frequently cited article in any field has extremely high academic value, and we found that among the top 10 papers in this study, the most frequently cited paper was paper 1: *Impact of the COVID-19 pandemic on mental health in the general population: A systematic review*, published in 2020. This paper presented a systematic review of the mental health hazards of COVID-19, and it was cited a total of 2095 times.

Analysis of keywords and hot research topics

In general, the co-occurrence of keywords (Figure 7A) revealed that 'humans', 'female', 'male', 'adult', 'adolescents', and

Table 3 Highly cited papers

	Ref.	Paper	DOI	TCs	TC per year	Normalized TC
1	Xiong *et al*[17], 2020	*J Affect Disorders*	10.1016/j.jad.2020.08.001	2095	523.75	84.06
2	Kramer *et al*[19], 2014	*P Natl Acad Sci USA*	10.1073/pnas.1320040111	1383	138.30	20.84
3	O'Keeffe *et al*[22], 2011	*Pediatrics*	10.1542/peds.2011-0054	1022	78.62	6.34
4	Gao *et al*[21], 2020	*Plos One*	10.1371/journal.pone.0231924	897	224.25	35.99
5	Dubey *et al*[16], 2020	*Diabetes Metab Syndr Clin Res Rev*	10.1016/j.dsx.2020.05.035	876	219.00	35.15
6	O'Keeffe *et al*[22], 2011	*Pediatrics*	10.1542/peds.2011-0054	834	64.15	5.18
7	Li *et al*[20], 2020	*Int J Env Res Pub HE*	10.3390/ijerph17062032	824	206.00	33.06
8	Kross *et al*[55], 2013	*Plos One*	10.1371/journal.pone.0069841	696	63.27	12.24
9	Schou Andreassen *et al*[18], 2016	*Psychol Addict Behav*	10.1037/adb0000160	685	85.63	17.38
10	Woods *et al*[23], 2016	*J Adolesc*	10.1016/j.adolescence.2016.05.008	534	66.75	13.55

TC: Total citation.

'social media' were the keywords with high centrality. These keywords occupied an important position in the network and were closely correlated with other terms. Among them, 'social media' was closely related to 'depression', 'mental health', 'COVID-19', and 'anxiety'; 'humans' was closely associated with demographic indicators such as 'female' 'male', 'adult', and 'adolescents', as well as with experimental methods such as 'cross-sectional studies', 'surveys', and 'questionnaires'.

A comparison of the co-occurrence of keywords before and after COVID-19 (Figure 7B and C) revealed variations in the hot research topics after COVID-19 period. Certain new keywords occurred (Figure 7C), including COVID-19-related keywords ('pandemic' and 'SARS-COV-2') and psychology-related keywords ('anxiety/epidemiology', 'depression/epidemiology', and 'stress'). In addition, some words were given additional weight, such as 'depression', 'anxiety', 'mental health', and 'cross-sectional studies', while other words decreased in proportion, including 'middle-aged'. Several terms even disappeared after COVID-19, including 'social support', 'social networking', 'Facebook', and 'olanzapine'.

We performed further clustering to estimate the relationships between the various keywords. The average silhouette width indicated the optimal number of keyword clusters (Figures 8A, 9A and 10A). Overall, the optimal number of keyword clusters was three (Figure 8A). Cluster 1 included illnesses and symptoms (blue), including 'schizophrenia', 'anxiety', 'depression', 'stress', and 'mental health'. Cluster 2 included 'children', 'students', 'aged', 'social media data', 'numerical data', and 'Internet' (red). Cluster 3 included research methods (*i.e.*, 'questionnaires', 'clinical studies', and 'cross-sectional studies') and COVID-19 (green; Figure 8B). The keyword heat map indicated that the COVID-19 pandemic was strongly associated with 'anxiety' and 'depression' (Figure 8C).

We then highlighted the distinct clusters influenced by COVID-19. Before COVID-19, the optimal number of clusters was three (Figure 9B), and olanzapine was strongly correlated with most keywords in the keyword heat map (Figure 9C). However, after COVID-19, the optimal clusters increased to five (Figure 10A). The first cluster (green) contained 'depression' and 'anxiety', while the second cluster (purple) contained 'article' and 'psychology'. The third cluster (blue) contained demographically classified words, such as 'adult', 'adolescent', and 'female'. The fourth cluster included 'humans'. The fifth cluster contained COVID-19-related words, such as 'COVID-19', 'pandemics', and 'surveys and questionnaires' (Figure 10B). After COVID-19, the word with the strongest correlations with other words was 'child', followed by 'COVID-19', 'depression', and 'mental health' (Figure 10C). Importantly, we identified keyword motor themes to help future researchers view research themes and core areas more comprehensively.

In general, 'humans', 'social media', 'female', and 'male' appeared consistently in the top-right 'motor themes' quadrant (Figure 11A-C), both before and after COVID-19, indicating that human behaviour, social media use, and gender differences have always been hot topics in research on psychopathology and social media use. Worryingly, there were completely different distributions of other themes before and after COVID-19. Before COVID-19 (Figure 11B), the motor themes in the top-right quadrant included 'olanzapine', 'risperidone', 'quetiapine', and 'treatment outcomes', indicating that the direction of treatment and clinical trials related to these drugs were important, well developed, and fundamental for the structuring of this research field. The top-left quadrant referring to niche themes included 'college students', and 'intervention', reflecting that although the research directions related to these keywords were relatively mature, they had little influence in the field of research on psychopathology and social media use. Emerging or declining themes, located in the bottom-left quadrant, included keywords relating to statistics and epidemiology, such as 'predictor', 'prevalence', and 'scale', suggesting that they were weakly developed and marginal. The lower-right quadrant, indicating basic themes - that is, important topics related to the fundamental framework of this field - included such keywords as 'clinical studies', 'Internet', and 'anxiety'; moreover, these keywords were located in close proximity to the motor themes, indicating that certain existing studies related to these keywords. However, these keywords were not explored in depth and should therefore be further investigated in the future. In addition, the keywords 'schizophrenia' and 'disease severity' appeared at the junction of the top-left and top-right quadrants, suggesting that the psychological

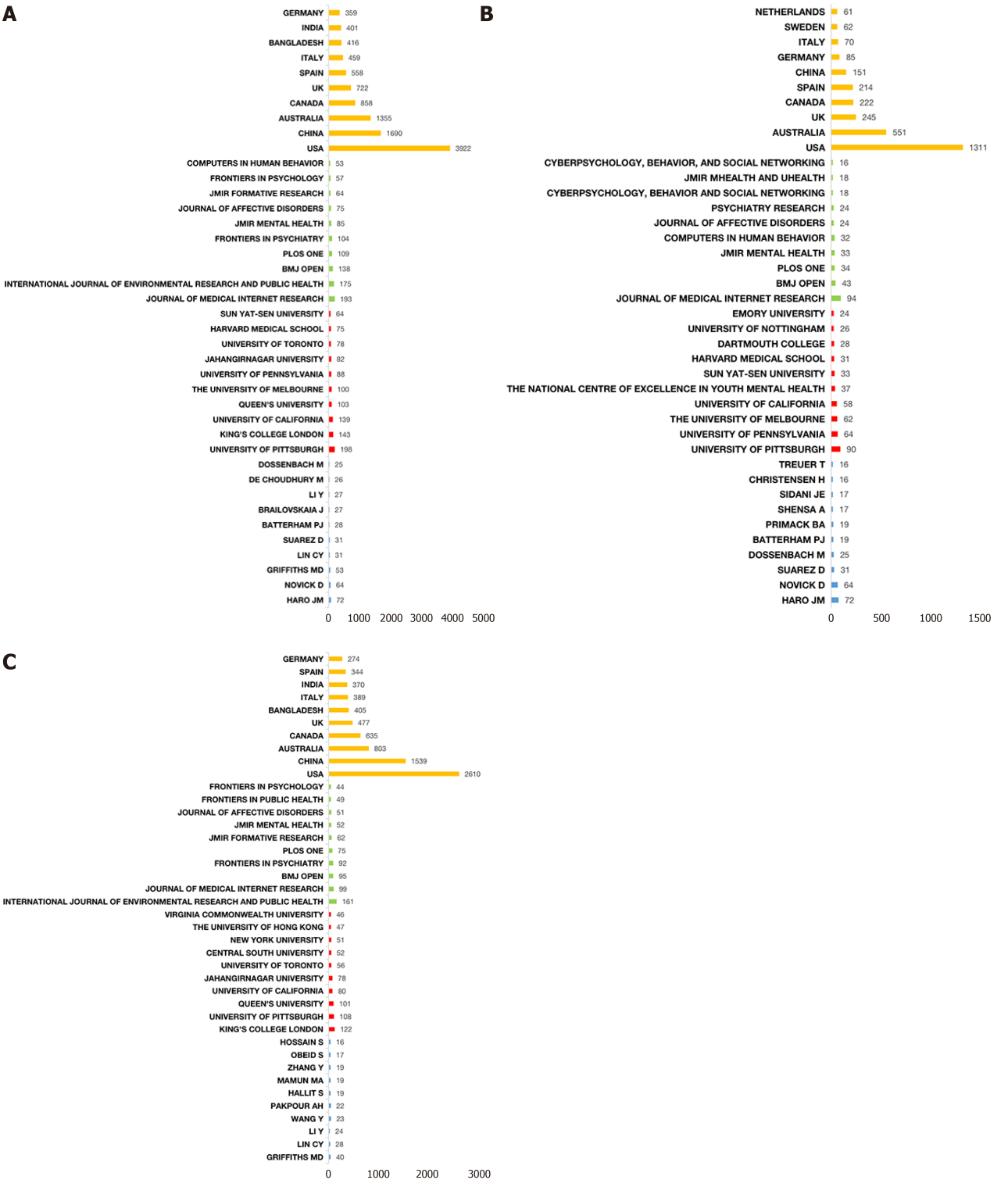

Figure 3 Ranking of high-yielding countries, journals, institutions, and authors. A: Outline of all the included studies; B: Studies before coronavirus disease 2019 (COVID-19) (1997-2019); C: Studies after COVID-19 (2019-2023).

problems caused by social media were gradually expanding and needed to be considered.

After the COVID-19 outbreak (Figure 11C), negative emotions became more widespread due to the long-term isolation, social distancing, declining income, and health damage caused by the pandemic. The term 'depression' became a hot topic in the motor theme quadrant. Words such as 'mental health', 'symptoms', and 'impact' appeared at the boundary between niche themes and emerging or declining themes. Keywords such as 'health', 'risk', and 'adolescents' appeared in emerging or declining themes, suggesting that such studies were going through periods of upswing or downswing. Keywords such as 'anxiety', 'prevalence', and 'stress' appeared at the boundary between emerging or declining themes and basic themes, suggesting that studies related to these keywords might move from one topic to another or make connections between different topics.

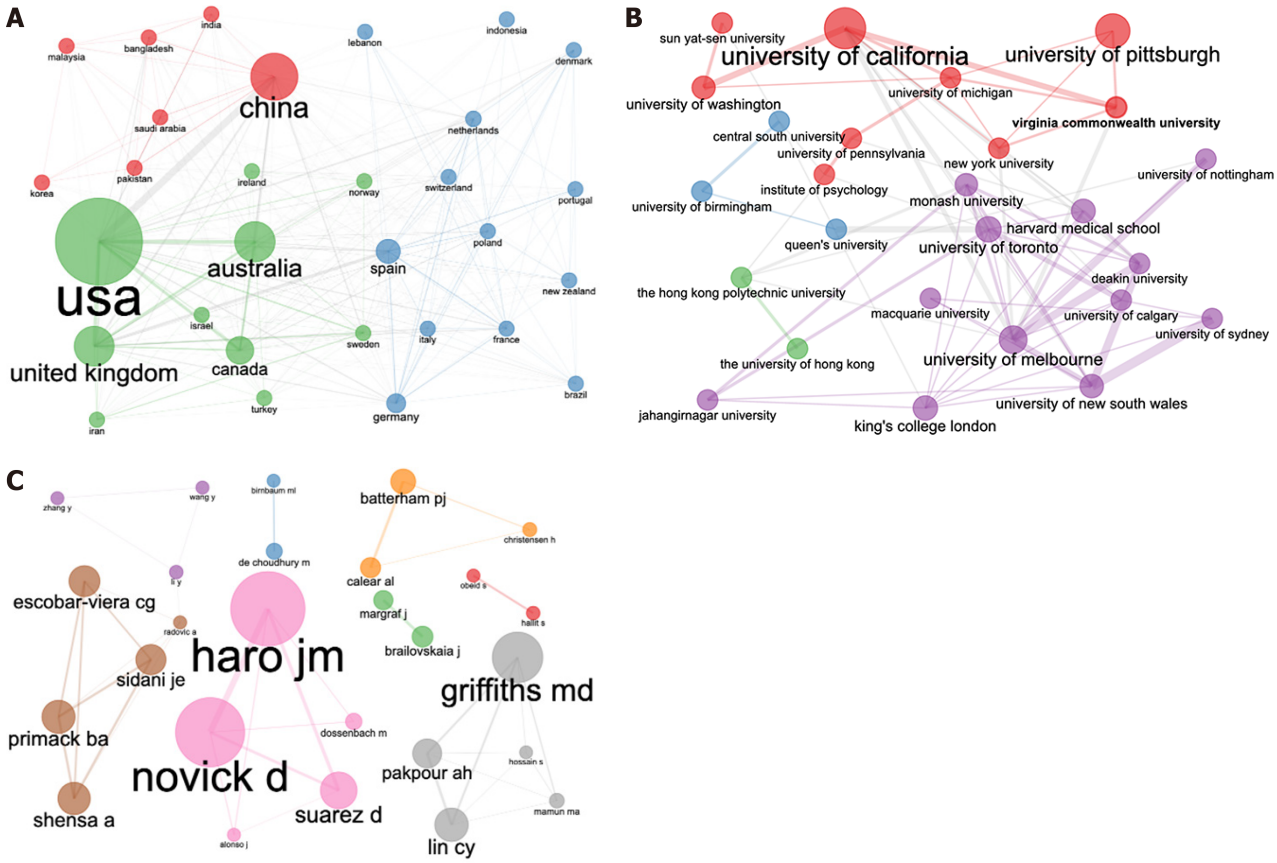

Figure 4 Outline of the entire global collaboration analysis. A: Country collaboration; B: Institutional collaboration; C: Author collaboration.

We further analysed the trends in the keywords. The discontinuous lines in Figure 12 represent the duration of a keyword burst, and the size of a circle represents the intensity of the burst. Keyword bursts can be roughly divided into three periods. In the first period (before 2010), the main keywords related to traditional medical treatments were 'olanzapine', 'quetiapine', and 'drug efficacy'. In the second stage (2011-2018), the main keywords were related to social media platforms and data mining (*i.e.*, 'Facebook', 'Internet/statistics', and 'social media/statistics'). In the third stage (after 2019), the main keywords were 'depression' and 'depression detection'. In addition, the keywords with the highest intensity were concentrated in studies published between 2019 and 2021.

DISCUSSION

Discussion: Implications and future research directions

A total of 4588 published papers were retrieved for our study, including 4350 research papers and 238 review papers (Figure 1). Research papers were published primarily in computer science and social behaviour journals, as well as medical and health sciences journals (Table 2). Among the top 10 most impactful journals for research on psychopathology and social media use, the *Journal of Medical Internet Research* (with the highest h-index) fell into the journal citation report quartile 1 (JCR Q1). This journal is the world's leading digital health journal, focusing on medical devices, applications, and related health education and clinical care. Altogether, we identified 12205 authors, 6616 research institutions, and 117863 references. In terms of authors and institutions, prolific authors and institutions were at the centre of the collaborative networks (Table 1, Figures 4-6). Furthermore, regarding the distribution by country, research on psychopathology and social media use was concentrated in developed countries, such as the United States, the United Kingdom, and Australia, while research collaboration was also led by these countries (Figures 3-6). This phenomenon could be partially explained by the fact that the internet was better developed in these countries, since Google, Microsoft, Apple, Facebook, and other internet giants were founded in the United States. According to a 2021 survey by the Pew Research Center, 48% of American adults said they obtained information from social media[24]. Internet users also produce large amounts of network information data, providing a wealth of information for scientific research purposes. However, high-income countries invest heavily in scientific research and devote more attention to psychopathology. For example, the United States (one of the countries that published the most papers) has relatively high per capita health expenditure, which reached $10784 in 2021[25]. The international cooperation network was also led by the United States (Figures 4-6), reflecting a global imbalance in the research output in this field. Developing countries produced fewer research publications, which did not mean they suffered less from social-media-induced mental illness. On the contrary,

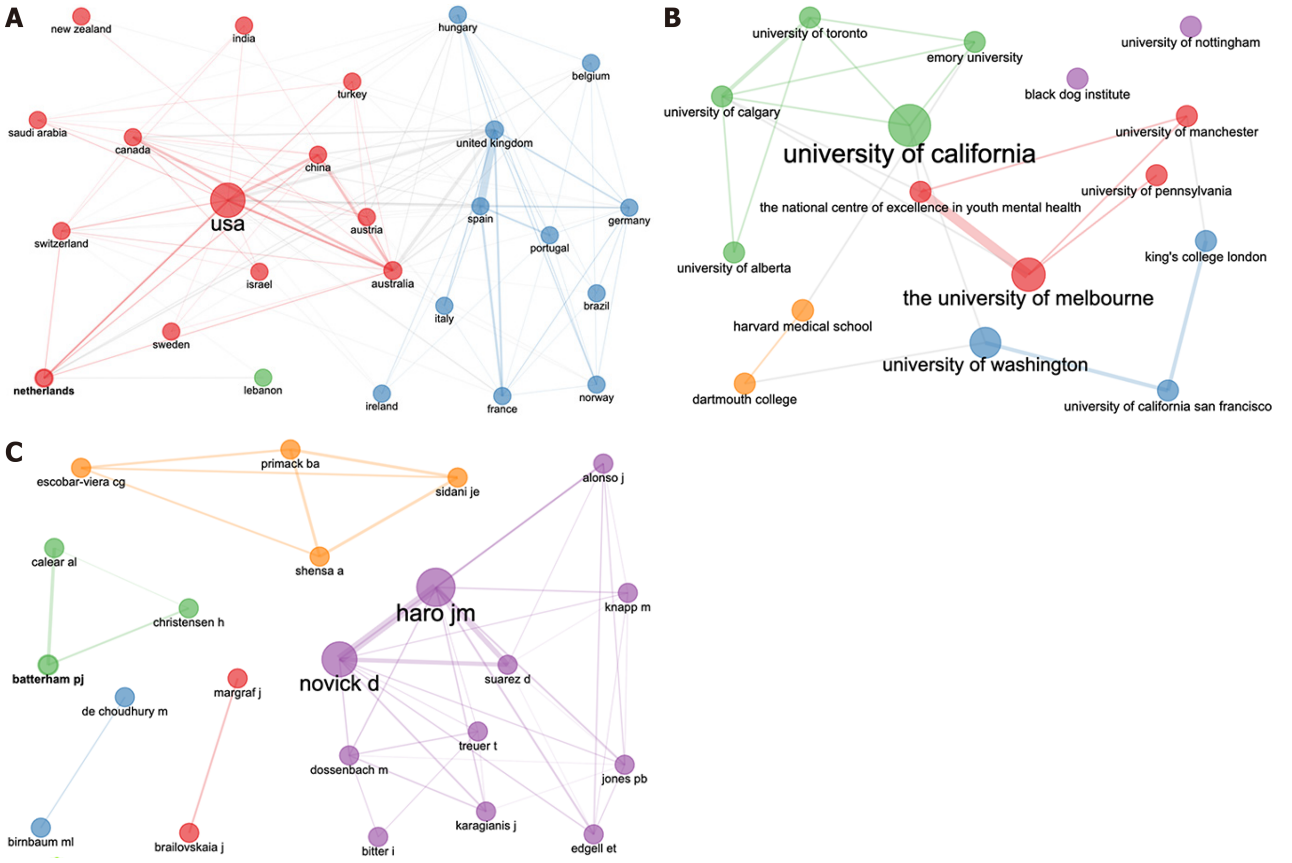

Figure 5 Global collaboration before coronavirus disease 2019 (1997-2019). A: Country collaboration; B: Institutional collaboration; C: Author collaboration.

social-media-induced internet addiction, anxiety, and depression are common in developing countries[26]. Therefore, cooperation between research groups in developing countries and those in developed countries would enable patients with social-media-induced mental illnesses to receive better medical care. Encouragingly, some developing countries, such as Bangladesh and China, have been expanding their investments in research on psychopathology and social media use. In addition, the comparison of the situations before and after COVID-19 revealed that Lebanon and South Africa, which had no collaboration with the other countries before COVID-19 (Figure 5), cooperated extensively with other countries after COVID-19 (Figure 6). Therefore, it can be inferred that research in this field will continue to develop significantly in the next few years. We further explored the possible subdivisions of the field through keyword analysis to provide references for future researchers.

We summarized the commonly used methods in research on psychopathology and social media use (Figures 7-10) and found that cross-sectional studies, questionnaires, and meta-analyses were the most commonly used methods. These research methods are traditional research methods in this field, and each has its own advantages. Cross-sectional studies are highly efficient, low cost, and can investigate multiple variables[27]; questionnaire surveys are anonymous, and the related data analysis is relatively easy[28]; meta-analyses are comprehensive and can provide extremely accurate findings [29]. However, these traditional methods also have certain limitations. In the case of a questionnaire survey, for example, the process of questionnaire completion, collection, and analysis is long and burdensome. Moreover, it is difficult to guarantee the compliance of the subjects and the reliability of the questionnaire completion, and the objectivity of the data may therefore be compromised. As can be seen from the second and third stages of the trends (Figure 12), an integrated approach that combines computational linguistics and clinical psychology is likely to become more popular in research on psychopathology and social media use in the future. For example, based on traditional psychological experimental and observational research, web crawlers could be used to collect data, and natural language processing could be used to analyse the psychological states and social interaction patterns of internet users and the impact of social media on different groups of people. These methods of information collection and analysis using big data align well with the characteristics of social media platforms. In addition, information analysis technologies based on artificial intelligence algorithms and models can accurately reflect the psychological states of internet users and reduce research costs. Similar approaches are useful for conducting complex, systematic large-scale experimental studies over long research periods, such as major clinical studies (Figure 11).

Through keyword analysis, in addition to the commonly used methods, we identified the main themes and progress in research on psychopathology and social media use. Our study found that mental illness was not affected by platform discrepancies, and the inappropriate use of any social media platform was likely to trigger pathological psychological states. Existing research has highlighted gender differences in social media use and psychopathological consequences (Figures 7-12) due to the differences in the biological structures and social media use patterns of men and women. Men's

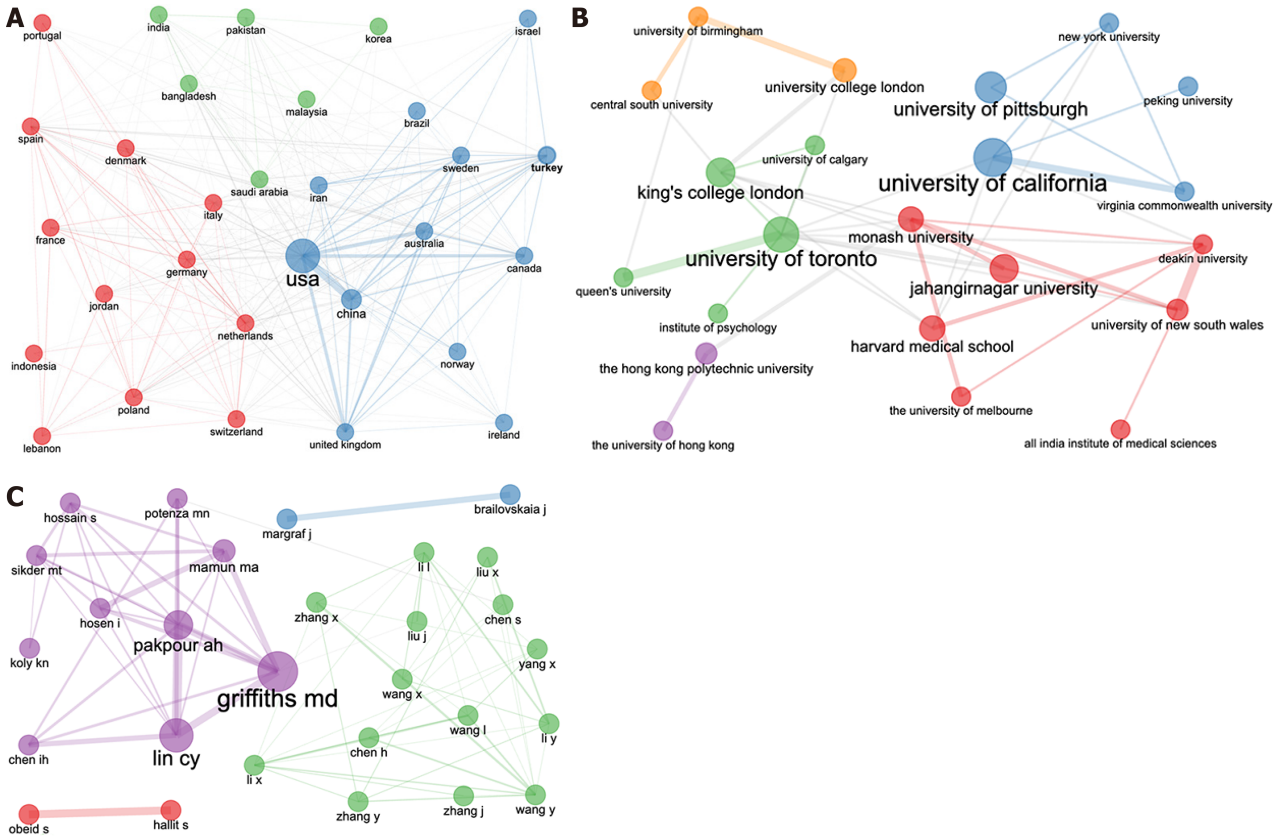

Figure 6 Global collaboration after coronavirus disease 2019 (2019-2023). A: Country collaboration; B: Institutional collaboration; C: Author collaboration.

androgen levels are higher than women's, making them likely to be excited by online sensory stimulation; therefore, they tend to use the internet and mobile apps for longer periods than women[30]. Some studies have found that men are better than women at spatial perception[31], hand-eye coordination[32], and competitive activities[33]. Therefore, they generally prefer sports, technology, politics, and other topics on social media[34], whereas women are more inclined to share family and personal details and other content on social media[35]. Consequently, men, and women face different mental health risks. Men are likely to fall into online game addiction, online gambling, and other destructive behaviours and are more psychologically dependent on the internet than women[36]. In addition, men who are often exposed to violence, pornography, profanity, and other negative content on social media platforms may tend to experience negative emotions, such as anxiety, depression, and anger. They may be unable to resist the temptation of such content and become addicted to it, which causes physical and mental damage[37]. Women may be more susceptible to social anxiety[38], and their negative self-images, perceptions, and behaviours may be significantly worsened by social media use. On the one hand, social media presents many images of beautiful, fashionably dressed women that may exert cultural pressure on females, resulting in women internalizing these standards for their external images to a significantly greater degree than men[26]. On the other hand, image consumption caused by consumerism attracts more women; capitalists encourage women to fall into a cycle of 'social aesthetic to appearance anxiety to body consumption' by presenting the external image they believe women should have. However, it is important to note that gender differences are not absolute. All people are independent individuals and exhibit different behaviours when using social media due to their own experiences, ideas, and interests. Therefore, we should not simply categorize people's social media use by gender or draw simple conclusions about the psychological harm a certain gender faces. Instead, we should devote more attention to individual personal characteristics and environmental factors, such as occupation, age, location, and economic status, in order to accurately understand their social media behaviour and help them solve the psychopathological problems they may face as a result.

Research has demonstrated that excessive use of social media is associated with anxiety, depression, low self-esteem, and internet addiction, which can negatively affect people's offline lives (Figure 7)[18,39]. Some researchers have studied psychopathological drug treatments, such as olanzapine[40], risperidone[41], and quetiapine[42]. Drug therapy has the advantages of convenience, efficiency, and speed, but it does not cure the root causes of the pathological problems caused by social media and may result in relatively severe drug dependence and side effects[43]; its limitations are therefore obvious. In recent years, with the steady transformation of the medical model from a traditional model to a bio-psychosocial one, psychosocial factors have increasingly been emphasized by scholars in this field, leading to the emergence of the 'social support' topical trend in 2017 (Figure 12) and the 'depression detection' burst in 2021. In recent years, with the rapid development of artificial intelligence and machine learning technology, traditional depression detection methods, such as psychological assessment, have been supplemented by new depression detection tools based

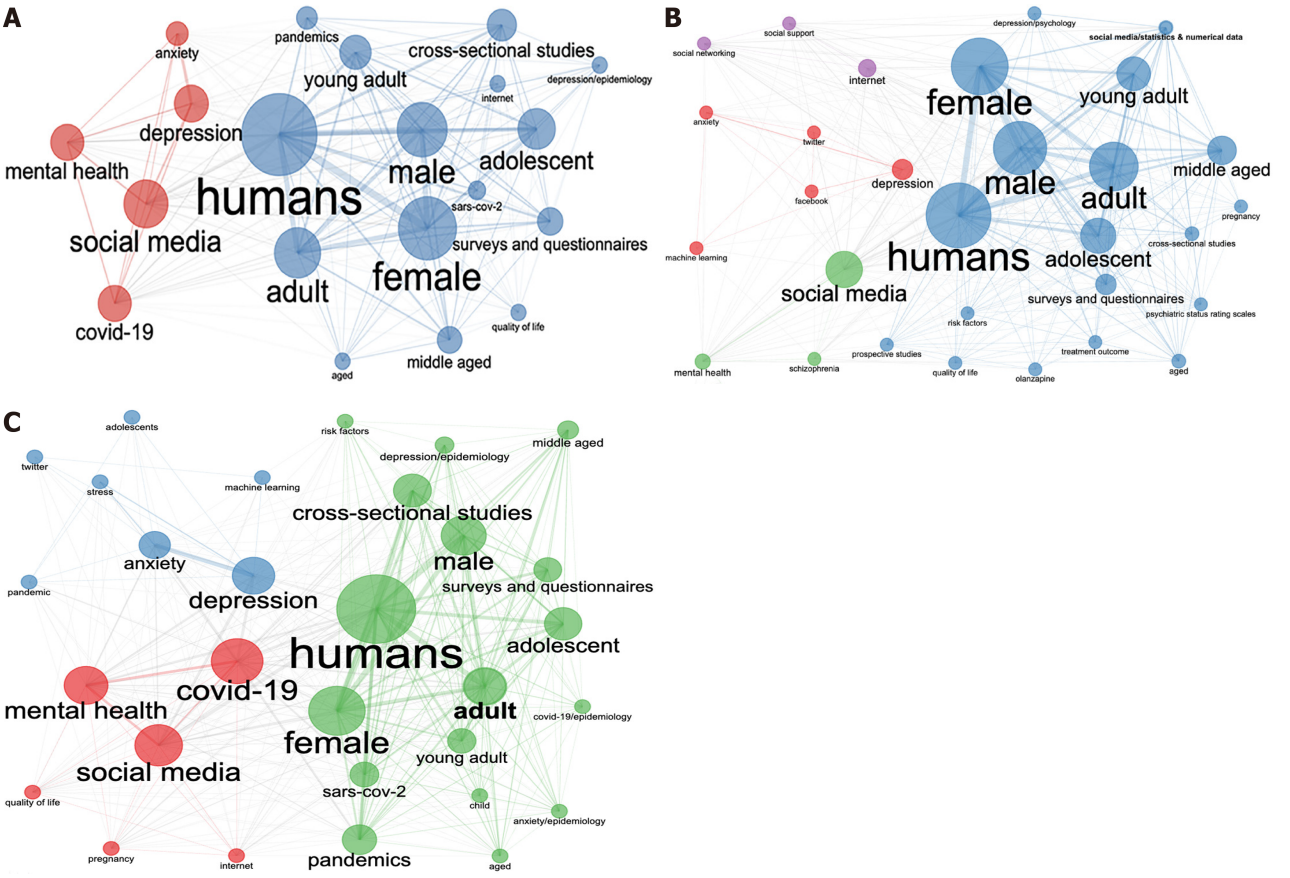

Figure 7 Co-occurrence of keywords. A: Overall co-occurrence of keywords; B: Co-occurrence of keywords before coronavirus disease 2019 (COVID-19) (1997-2019); C: Co-occurrence of keywords after COVID-19 (2019-2023).

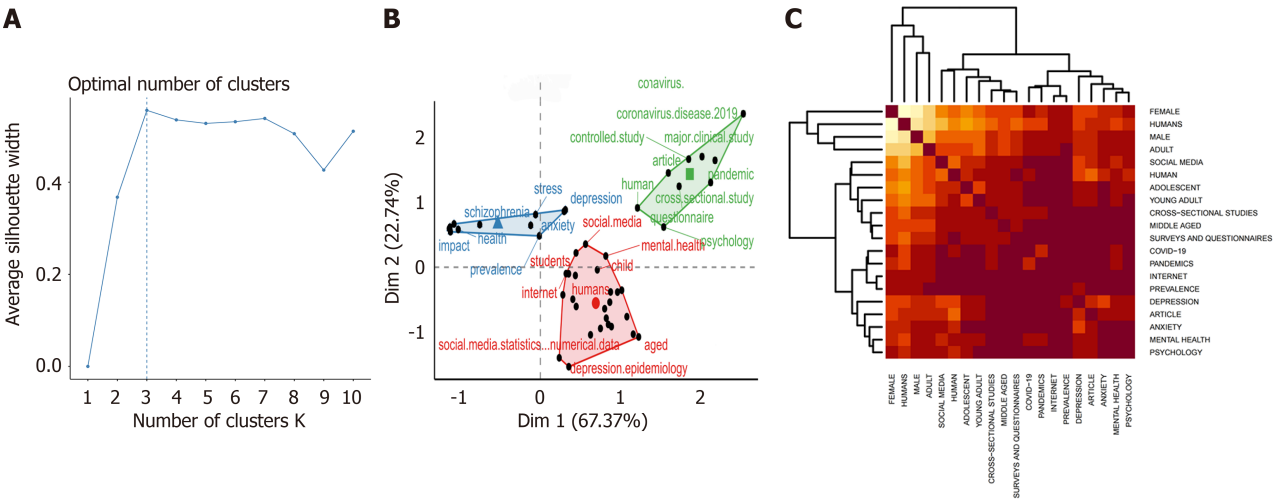

Figure 8 Outline of the complete keyword cluster and heat map analysis based on the topics of research on psychopathology and social media use. A: Optimal clustering number identified; B: Three clusters identified; C: A heat map used to assess the association strength of the keywords.

on data analysis and algorithmic models[44]. These tools can determine whether a person is depressed by analysing various data, including voice, text, and images, thus providing doctors with faster and more accurate diagnosis and treatment recommendations. Neurobiological[45] or sociological[46] approaches also offer new hope. Neurobiological methods, such as electrotherapy and magnetic therapy, can help alleviate depression and anxiety symptoms by stimulating neuronal activity[47], and neurofeedback, such as electroencephalography, can support patients' self-regulation[48]. In addition, from a sociological perspective, it is extremely important to detect and evaluate patients' interpersonal and family problems and guide them in effectively coping with work, financial, and interpersonal pressures when treating certain illnesses, such as depression (Figure 8). Future researchers should conduct a more in-depth exploration of these aspects.

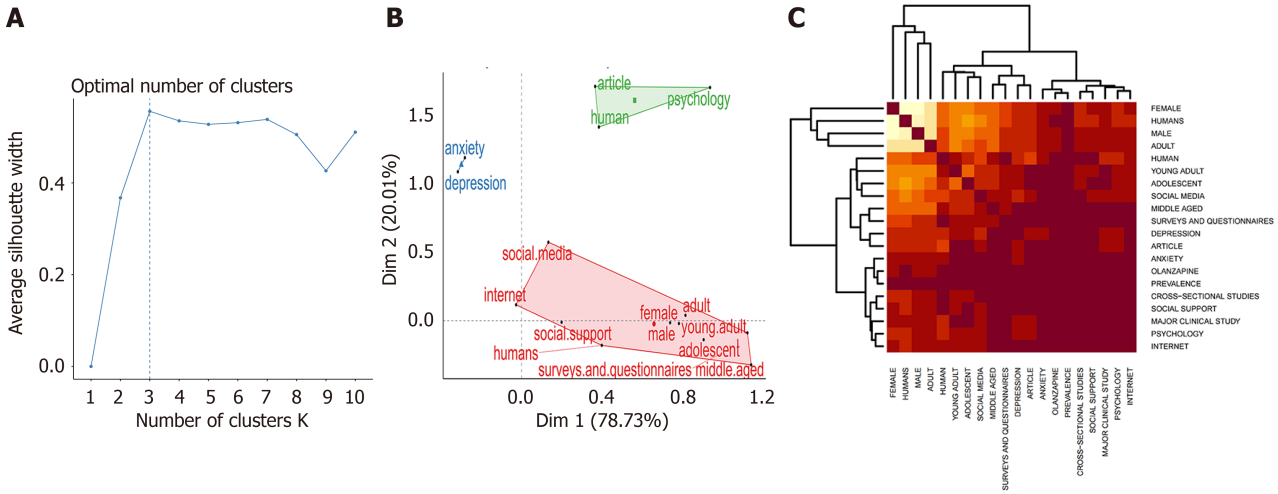

Figure 9 Keyword cluster and heatmap analysis based on the topic of research on psychopathology and social media use before coronavirus disease 2019 (1997-2019). A: Optimal clustering number identified; B: Three clusters identified; C: Heat map used to assess the association strength of the keywords.

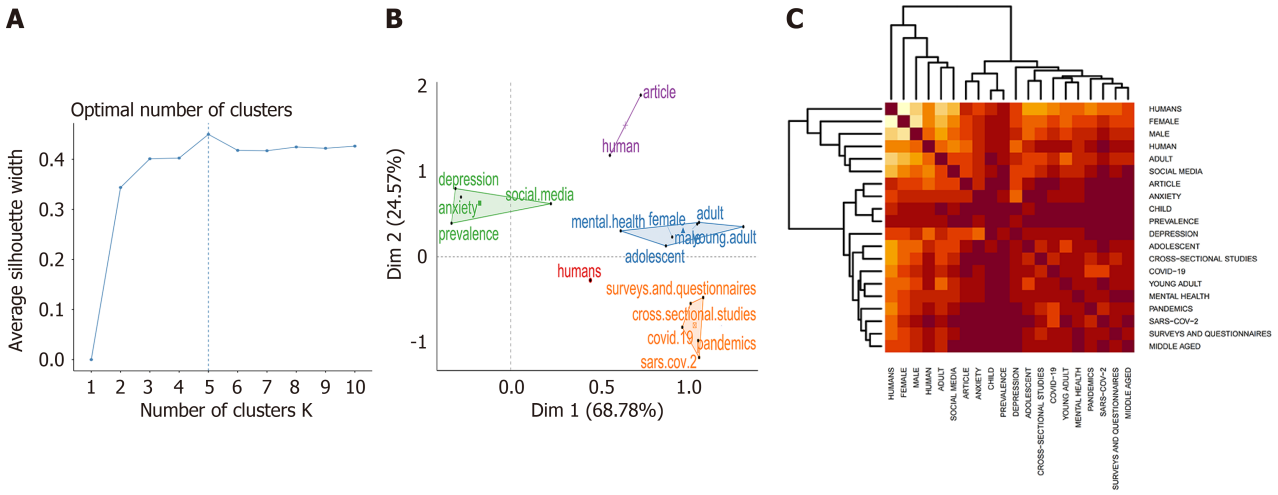

Figure 10 Keyword cluster and heatmap analysis based on the topic of research on psychopathology and social media use after coronavirus disease 2019 (2019-2023). A: Optimal clustering number identified; B: Five clusters identified; C: Heat map used to assess the association strength of the keywords.

In addition, it is worth noting that COVID-19 is a very important emerging direction for research on psychopathology and social media use. There was a huge difference in literature output before and after COVID-19, and a surge after COVID-19 (Figure 2). The co-occurrence of keywords (Figure 7) demonstrated that COVID-19 was strongly correlated with anxiety and depression. The use of social media increased dramatically during the COVID-19 pandemic due to social media becoming an important channel for people to obtain information, exchange emotions, and relieve psychological pressure[49]. However, social media is laden with negative information, disinformation, and rumours, and constant exposure to this information can trigger feelings of anxiety and depression. During COVID-19, people may have felt that they could not present positive images of their lives and achievements to others on social media[50], resulting in anxiety and depression due to social comparisons and self-burden issues. Overreliance on social media and neglect of offline social interactions also caused anxiety and depression during COVID-19[51]. Moreover, the onset of anxiety and depression is related to people's excessive concern and fear of coronavirus disease, with this corona-phobia likely stemming from the unknown nature of the virus, panic over the disease, or reactions to the overwhelming spread of alarming information on social media. This has significantly influenced the public's response to the COVID-19 pandemic. The complex psychological states fostered by social media platforms during the pandemic made the formulation and implementation of psychological interventions particularly important, and social media offered a platform for health promotion. If academics and healthcare professionals can effectively identify the needs of patients on social media platforms and provide timely interventions, similar public health emergencies may be prevented from causing widespread mental disorders.

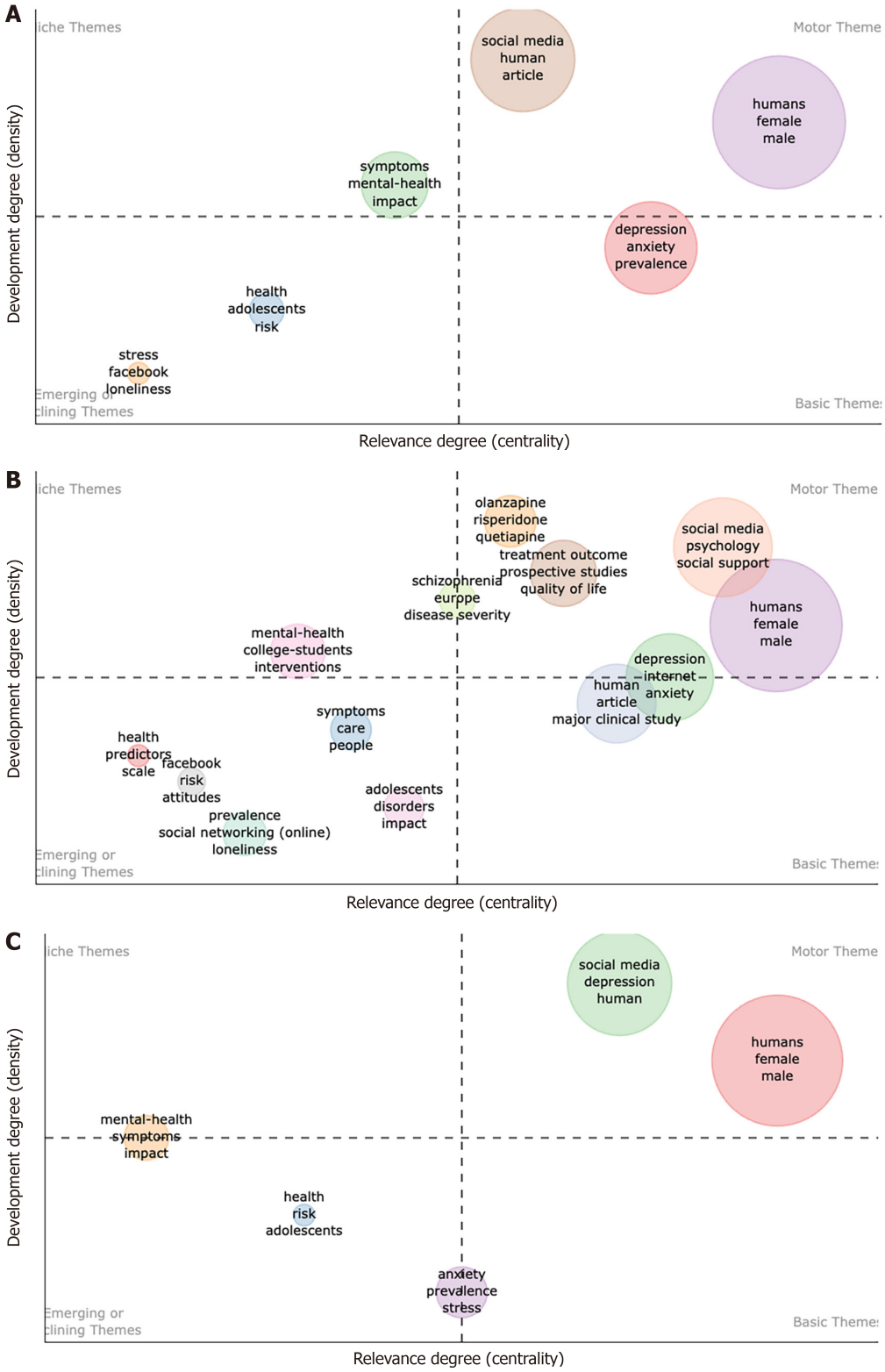

Figure 11 Thematic maps. A: Overall thematic map; B: Thematic map before coronavirus disease 2019 (1997-2019); C: Thematic map after COVID-19 (2019-2023).

After COVID-19, the term 'child' became a hot topic in research on psychopathology and social media use, as presented in Figure 7C, and was strongly associated with most keywords, as presented in Figure 10C. Social media use during COVID-19 could have either positive or negative effects on children's psychology. After the COVID-19 outbreak, longer durations of daily video streaming and video chat were associated with higher prosocial scores. Social media could help children stay connected with friends and family and alleviate the loneliness caused by social isolation[52]. However, console games, mobile apps/games, and video-sharing platforms tend to be associated with greater problematic media use[53], and excessive use of social media can lead to addiction and affect children's time-management skills. This can cause them to neglect important activities, such as studying, outdoor activities, and social

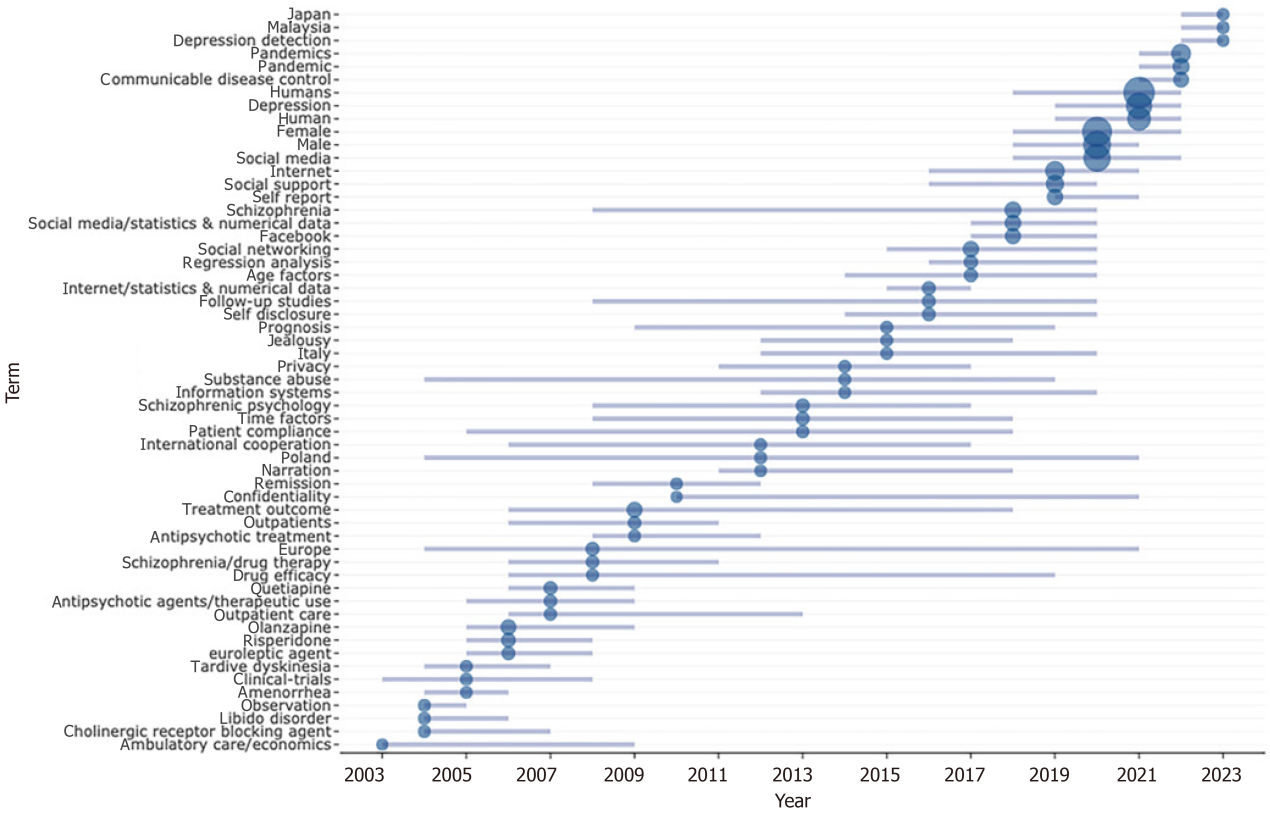

Figure 12 Trends in research on psychopathology and social media use.

interactions, leading to anxiety, depression, and impaired self-esteem[54]. Therefore, parents and guardians should provide appropriate guidance and supervision when children use social media to ensure that they are able to use social media properly and to avoid potential negative effects.

This study did have certain limitations. First, we retrieved English-language papers only, which may have led to bias in language selection and some valuable non-English-language papers being missed. In addition, we selected only the WOSCC, PubMed, and Scopus databases as data sources; other platforms were not used. Despite these limitations, we have included most of the global studies in this field, and through bibliometric evaluation, we have suggested implications for future research on psychopathology and social media use based on empirical evidence.

CONCLUSION

This is the first bibliometric study to systematically analyse research on pathology and social media use. We identified prolific authors, institutions, and journals in this field, and went on to identify current collaboration networks, research frameworks, and trends through keyword analysis. The main topics in this field focused on specific mental illnesses, populations, and clinical treatments, and we observed that research on gender differences in psychopathological states was relatively mature. In the future, more in-depth clinical studies should be conducted, and more advanced artificial intelligence algorithms and models should be applied. In addition, more attention should be paid to psychopathological prevalence and detection targeting different groups of people. The research results reflected an increased level of concern about mental health issues after COVID-19 and a changing emphasis on social media use and the impact of public health emergencies. We hope that this study will provide useful insights to enable health managers, psychologists, and other health workers to determine future research directions and encourage them to better utilize social media platforms for their professional work, such as health policy advocacy, peer communication, and crisis intervention for mental illness. Future researchers should continue to strengthen their international cooperation, explore research methods that align with the information age, and develop novel treatments for mental illnesses caused by social media.

FOOTNOTES

Author contributions: He RQ, Dai J, Huang H, Yang Z, Kong JL, and Chen G designed the research; Zhang MD and Wei JY searched, downloaded, and organized the raw data, and extracted and calculated the data; He RQ and Chen G analyzed and summarized the results; Zhang MD, Luo JY, Huang WY, and Wei JY wrote the first draft of the manuscript; Zhang MD, He RQ, Dai J, Huang H, Yang Z, Kong JL, and Chen G revised the paper.

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