

World Journal of *Psychiatry*

World J Psychiatry 2024 June 19; 14(6): 760-998



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INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJP* as 3.9; JIF without journal self cites: 3.8; 5-year JIF: 3.7; JIF Rank: 58/276 in psychiatry; JIF Quartile: Q1; and 5-year JIF Quartile: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xin-Xin Che*, Production Department Director: *Xu Guo*; Cover Editor: *Jia-Ping Yan*.

NAME OF JOURNAL

World Journal of Psychiatry

ISSN

ISSN 2220-3206 (online)

LAUNCH DATE

December 31, 2011

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Ting-Shao Zhu

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3206/editorialboard.htm>

PUBLICATION DATE

June 19, 2024

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Fentanyl and xylazine crisis: Crafting coherent strategies for opioid overdose prevention

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Specialty type: Psychiatry

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Cheng J, China

Received: January 1, 2024

Revised: May 6, 2024

Accepted: June 4, 2024

Published online: June 19, 2024

Processing time: 170 Days and 11.4 Hours



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Abstract

The United States is in the throes of a severe opioid overdose epidemic, primarily fueled by the pervasive use of fentanyl and the emerging threat of xylazine, a veterinary sedative often mixed with fentanyl. The high potency and long duration of fentanyl is compounded by the added risks from xylazine, heightening the lethal danger faced by opioid users. Measures such as enhanced surveillance, public awareness campaigns, and the distribution of fentanyl-xylazine test kits, and naloxone have been undertaken to mitigate this crisis. Fentanyl-related overdose deaths persist despite these efforts, partly due to inconsistent policies across states and resistance towards adopting harm reduction strategies. A multifaceted approach is imperative in effectively combating the opioid overdose epidemic. This approach should include expansion of treatment access, broadening the availability of medications for opioid use disorder, implementation of harm reduction strategies, and enactment of legislative reforms and

diminishing stigma associated with opioid use disorder.

Key Words: Fentanyl; Xylazine; Opioid overdose; Epidemic; Opioid use disorder; Buprenorphine; Medications for opioid use disorder

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Core Tip: This editorial addresses the escalating opioid overdose crisis in the United States, exacerbated by the use of fentanyl and the emerging threat of xylazine. Despite efforts like enhanced surveillance and distribution of test kits and naloxone, fentanyl-related deaths persist due to inconsistent state policies and resistance towards harm reduction strategies. The paper advocates for a multifaceted approach, including expanded treatment access, wider availability of medications for opioid use disorder, implementation of harm reduction strategies, legislative reforms, and reducing stigma associated with opioid use disorder.

Citation: Jain L, Kaur J, Ayub S, Ansari D, Ahmed R, Dada AQ, Ahmed S. Fentanyl and xylazine crisis: Crafting coherent strategies for opioid overdose prevention. *World J Psychiatry* 2024; 14(6): 760-766

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/760.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.760>

INTRODUCTION

The deadly implications of fentanyl in the drug crisis: Fentanyl has recently emerged as a major risk factor and potentially leading cause of overdose deaths among people aged 18 to 45, with fatalities exceeding roughly 150 deaths per day in the United States alone^[1,2]. This synthetic opioid, initially developed for medical purposes such as pain, anesthesia, and palliative care, is roughly 50 to 100 times more potent than heroin and morphine. Fentanyl has widely infiltrated the illicit drug market and is often mixed with other substances. It has been found to be augmented illicitly with heroin, cocaine, methamphetamine, and even counterfeit pills are manufactured that mimic prescription opioids such as oxycodone, alprazolam, or stimulants like amphetamines^[2,3]. Illicit production of fentanyl occurs in countries like China, India and Mexico; but sometimes drug traffickers manufacture their own fentanyl in the United States with precursor chemicals sourced from China and Mexico^[3]. Fentanyl has become a primary driver in increasing overdose deaths due to its deceptive appearance and significant potency^[2,3]. Many users consume it unknowingly, significantly increasing the likelihood of rapid and fatal overdoses despite education efforts. In the contemporary discourse on public health, the escalating incidence of fatalities linked to fentanyl and other synthetic opioids is a subject of profound concern. In 2021, synthetic opioids were implicated in 88% of 80411 opioid overdose deaths, which constituted 75.4% of all drug overdose fatalities, highlighting the urgent need to address the growing crisis of opioid-related overdoses^[1,2].

Fentanyl's unique pharmacological characteristics pose significant challenges when it comes to the management and treatment of opioid overdose. As a powerful synthetic opioid, fentanyl has a high affinity for opioid receptors, leading to its rapid and intense onset of effects. This rapid onset is mitigated by fentanyl's quick redistribution to other tissues leading to a short duration of action. This effect is due to differences in lipophilicity, with fentanyl being lipid soluble and other drugs such as morphine being more hydrophilic^[4]. As a consequence, a higher dose of naloxone (10-fold higher) is required to reverse the effects of fentanyl as compared to morphine. Even low doses of fentanyl show decreased sensitivity to reversal by naloxone^[5].

The pharmacological profile of fentanyl presents unique challenges in the treatment of opioid use disorder (OUD). Fentanyl's high potency and its user's quick development of high tolerance leads to severe cravings. These characteristics reduce response to low to moderate doses (8-16 mg) of life-saving medications such as buprenorphine^[6]. A recent retrospective cohort study published in *JAMA* notably found that patients prescribed 24 mg of buprenorphine had a significantly lower risk of treatment discontinuation compared to those prescribed 16 mg (adjusted hazard ratio, 1.20; 95% confidence interval: 1.06-1.37)^[6]. Patients prescribed 24 mg of buprenorphine were observed to have a better retention in treatment than patients prescribed 16 mg of buprenorphine. The current guidelines suggesting a daily maintenance target dose of 16 mg were established prior to the advent of fentanyl and appear to be insufficient in control of cravings and withdrawal associated with its use. Some studies from the past have indicated that the benefits of buprenorphine may increase with daily doses of up to 32 mg^[6,7]. This highlights the urgent need for tailored treatment approaches in cases of fentanyl use, possibly requiring higher doses of buprenorphine or alternative treatments like methadone to manage the condition effectively.

WHY DO WE NEED RADICAL REFORMS

In the United States, individuals struggling with OUD often encounter obstacles in accessing treatment options. This issue

is largely due to the hesitation among lawmakers, public health agencies, and clinical providers to fully endorse ‘harm reduction’ as a viable approach to treatment. Despite evidence supporting the efficacy of harm reduction, there continues to be a struggle for acceptance and implementation. A collaborative study by NIDA (National Institutes of Health) and the Centers for Disease Control and Prevention’s National Center for Injury Prevention and Control found that in 2021 around 2.5 million adults in the United States suffered from OUD, but only 36% received substance use treatment, and just 22% received OUD-specific medications. This left an overwhelming 78% of adults with OUD without essential OUD treatment[8].

The gap in treatment is partly explained by systemic challenges such as the aforementioned decision makers (lawmakers, public health agencies, and clinical providers) often harboring internalized negative attitudes and beliefs toward people with OUD. These attitudes can affect the adoption of globally recognized effective treatment strategies[9]. Moreover, medications for OUDs (MOUDs) itself faces prejudice and stigma at a cultural level, adding further barriers to their acceptance as a treatment option[10]. Compounding these issues is the operational model of many opioid treatment programs (OTPs) in the United States, which is often described as adhering to a “high threshold, low tolerance” approach[11]. This model is characterized by substantial initial barriers to treatment entry (‘high threshold’), making it challenging for patients with OUD to access necessary care. These programs also exhibit a ‘low tolerance’ for patient lapses or non-compliance, resulting in a propensity for swift removal of patients from treatment for minor transgressions. This model not only impedes the initiation of treatment but also jeopardizes the continuity and effectiveness of care for those with OUD who manage to overcome the initial hurdles[11]. This ‘high threshold, low tolerance’ attitude also extends to individuals who use illicit fentanyl, further complicating the treatment landscape and influencing decision-making processes. While there is advocacy from some decision-makers for increased access to safer alternatives and enhanced safety measures for people with OUD using fentanyl, many favor a more punitive approach, viewing legal action as a primary tool to combat the fentanyl crisis. The ‘high threshold, low tolerance’ model in many OTPs particularly affects individuals using fentanyl. For example, the stringent entry requirements often mean that individuals using fentanyl face considerable hurdles in accessing treatment such as extensive documentation, prerequisite counseling sessions, or detoxification requirements. Once in treatment, minor infractions such as missing appointments, relapsing, or positive drug tests can lead to dismissal from the program. This approach fails to acknowledge the chronic nature of OUD and the complex set of challenges faced by individuals in recovery. The lack of flexibility and understanding within these programs can result in individuals being ejected from treatment for relatively minor setbacks, which are often part of the recovery process.

Due to the widespread availability of fentanyl in the illicit drug supply, people are actively encouraged to test their opioids prior to consumption. The use of sterile injection supplies, naloxone, and fentanyl test strips is promoted as well [12-14]. Unfortunately, the potential benefits of each of these interventions are mitigated by significant barriers. The use of fentanyl testing strips remains a hurdle[15], with people facing challenges acquiring the test strips due to state laws banning their possession[12]. Apart from protection from overdose, injection drug users with a positive fentanyl test strip, are five times more likely to alter their drug use behavior[16].

Another set-back when combating the opioid crisis is limitations to needle and syringe programs in various parts of the United States, especially rural areas[17]. Although the number of programs has increased across the country, these programs face operational challenges and communities continue to struggle to deliver health and social services to drug users[18].

The North American Drug Checking Survey was conducted in 2022 to evaluate drug-checking services available for people who use drugs. This survey identified significant barriers to drug-checking services like poor staffing (50%), lack of funding (88%), and absence of technical expertise (38%). The survey also highlighted how drug-checking services are significantly impacted by local and state laws banning the possession and/or distribution of illicit drug samples, drug paraphernalia, or drug-checking equipment[19].

A study carried out in 2017 found a notable decline in opioid-related deaths following the passing of Naloxone Access and Good Samaritan laws[20]. Several barriers to naloxone distribution persist. These barriers include institutional rules, state regulations, stigma, cost, and lack of educational training. The presence of these barriers indicates that there is a crucial need for improvement in the use of naloxone for overdose prevention[21]. A recent review found that naloxone availability varies significantly among different pharmacies. The study evaluated around 11000 audited pharmacies and found that 37.2% did not have naloxone in stock and 48.1% did not have naloxone immediately accessible upon request. Despite a recent ruling that allowed naloxone to be dispensed without a prescription, 37.1% of pharmacies indicated they were not willing to do so[22]. Hence, radical reforms are required to curb the existing fentanyl epidemic. Despite significant willingness to use overdose prevention sites and/or supervised consumption sites among people who use opioids, several local governments are either reluctant to consider creating such sites or face significant challenges in creating these sites for people who use opioids[23,24].

DISCUSSION AND RECOMMENDATIONS

Recent statistics released by the Centers for Disease Control and Prevention’s National Center for Health Statistics reveal a concerning trend in drug overdose deaths in the United States. Over a 12-month period ending in May, the number of fatalities due to drug overdoses surpassed 112000 cases. This finding reflects an increase of approximately 2.7% from the previous year’s figure of 109261 deaths[2]. The data also highlights that the crisis disproportionately affects young individuals and communities of color, underlining the urgent need for targeted interventions and support in these populations. The continuously changing landscape of the opioid crisis is marked by the emergence of new and serious

threats. One such threat is the $\alpha 2$ adrenergic agonist animal tranquilizer xylazine[25]. Xylazine has been detected in increasing numbers of overdose deaths, and it is known to cause severe and long-lasting flesh wounds in its users[26-28]. In addition, the advent of nitazenes, a class of synthetic opioids, introduces a new level of risk to the crisis[29,30]. Nitazenes could potentially be more potent than fentanyl, already notorious for its own extreme potency[31-33]. The introduction of these substances into the drug market intensifies the complexity of the opioid crisis. This concern adds another layer of difficulty to the formidable task of curtailing opioid misuse and overdose incidents, underscoring the urgent need for comprehensive strategies and interventions. The pervasive use of fentanyl not only has severe health repercussions but also significant socio-economic impacts. These include increased healthcare expenditures due to the necessity for emergency overdose treatments, frequent hospitalizations, long-term addiction care and loss of lives, as well as broader societal costs such as diminished productivity and greater demands on the criminal justice system. Such challenges highlight the need for comprehensive public health strategies. Effective measures could include enhanced surveillance systems, the widespread availability of naloxone, and educational programs aimed at healthcare providers and the general public about the dangers of fentanyl and effective management practices. Implementing these initiatives can alleviate the direct economic impact and foster improvements in community health outcomes.

The mental health implications of drug use are substantial, with a notable rise in psychiatric disorders. The impact on mental health is further exacerbated when fentanyl is combined with other substances, such as stimulants or xylazine, compounding the severity of these effects. Addressing this aspect requires both preventive and therapeutic strategies, underscoring the importance of accessible mental health services and robust support systems. At an international level, addressing the spread of fentanyl transcends national boundaries and requires concerted global cooperation. Strengthening international partnerships, particularly with key countries in the fentanyl supply chain, is vital. Enhanced diplomatic efforts, such as those between the United States and China, which led to the recent reconvening of the United States-China counternarcotics commission[34], are critical steps towards mitigating the challenges posed by fentanyl production and trafficking. These collaborative efforts are essential for crafting effective strategies that can save lives and stabilize affected communities globally.

Given the increasing complexity and severity of the crisis, a multi-dimensional approach is vital. Public health strategies must evolve to address the changing nature of substance abuse. This includes consolidating harm reduction services by increasing access to naloxone, promoting needle exchange programs, offering MOUD, and providing testing strips for substances like fentanyl and xylazine. The implementation of mobile methadone clinics and the modernization of methadone treatment would also offer flexible and accessible care[35]. The opioid crisis has disproportionately impacted certain segments of the population, particularly marginalized groups such as African American individuals and other people of color[36-38]. These communities often face significant barriers to accessing healthcare services, including MOUDs. Mobile narcotic treatment programs operating through vans that travel to multiple locations are crucial in delivering methadone treatment to these underserved populations[39], mitigating barriers such as transportation access, long travel distances, and stigma.

The integration of digital health technologies such as mobile medical apps and telemedicine plays a crucial role in expanding reach and enhancing treatment plans. Technologies like wearable health monitors, artificial intelligence-powered analytics, and innovative approaches such as the Wheels and Waves VDOT program as well as smart drug dispensers contribute to improved treatment adherence and reduced misuse[40]. Virtual reality therapy offers a novel method for psychological support and relapse prevention. Integrating services with social determinants of health like housing and employment services and genetic testing are key to personalized treatment approaches.

As we continue to grapple with the opioid crisis, innovative approaches are being explored. These approaches include the implementation of safe consumption sites (SCS)[23,24]. These facilities offer a controlled environment where individuals can consume drugs under medical supervision with the aim of reducing overdoses and infectious disease transmission. These sites are not without controversy. Legal pushback and public criticism are commonly encountered in their implementation. Critics argue that saline infusion sonography (SIS) may enable drug use rather than deter it and could potentially lead to an increase in neighborhood crime. The legality of SIS under federal law is currently being contested which adds another layer of complexity to the issue. It is crucial to continue evaluating the effectiveness of SIS and other harm-reduction strategies. As the opioid crisis continues to evolve, so too must our approach to addressing it. It is necessary to center our approach on evidence-based practices and a commitment to improving public health.

Policy reforms and targeted programs are essential in the comprehensive fight against the opioid epidemic. Essential steps include expanding insurance coverage for addiction treatment, enforcing mental health parity laws, and developing programs targeting emerging threats such as xylazine and nitazenes. A comprehensive response also encompasses broadening the scope of services to support mental health and social needs, reinforcing harm reduction strategies such as needle and syringe programs, overdose education and naloxone distribution, SCS, and drug checking services[41-43]. These strategies offer practical ways to reduce the direct and indirect harm associated with substance use and are crucial in mitigating the immediate risks of drug use while providing long-term support for individuals battling addiction. Lastly, addressing the stigma associated with substance use disorders is vital. Efforts to reduce stigma such as nationwide anti-stigma campaigns and the promotion of person-centered language when discussing substance use can foster a supportive environment for those seeking help and enhance treatment outcomes[44]. Educational campaigns aimed at raising awareness about the dangers of potent new substances are crucial.

CONCLUSION

Addressing the fentanyl crisis is a complex and interconnected challenge that demands a comprehensive response.

Overcoming the stigma associated with addiction, expanding access to evidence-based treatment, and advocating for harm reduction initiatives are central to tackling this epidemic effectively. This multifaceted crisis also involves issues such as polydrug use, limited treatment accessibility, and criminal justice reform. A collaborative effort is essential and must involve healthcare providers, policymakers, communities, and individuals affected by fentanyl use. Other vital components of this response include public awareness, education, and comprehensive data collection. By addressing these challenges holistically and working together, we can make meaningful progress in reducing the harm caused by fentanyl and preventing further devastation to individuals and society.

FOOTNOTES

Author contributions: All authors made significant contributions to this paper; Ahmed S designed the overall concept and outline of the manuscript; Jain L, Kaur J, Ayub S, Ansari D, Ahmed R, and Dada AQ contributed to the discussion and design of the manuscript; and all authors contributed to the writing, editing of the manuscript, illustrations, and literature review.

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

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Che XX

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Metabolic complications of psychotropic medications in psychiatric disorders: Emerging role of *de novo* lipogenesis and therapeutic consideration

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Specialty type: Psychiatry

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade C

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade B, Grade B

P-Reviewer: Chen K, China

Received: January 6, 2024

Revised: May 5, 2024

Accepted: May 23, 2024

Published online: June 19, 2024

Processing time: 165 Days and 11.9 Hours



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Abstract

Although significant advances have been made in understanding the pathophysiology of psychiatric disorders (PDs), therapeutic advances have not been very convincing. While psychotropic medications can reduce classical symptoms in patients with PDs, their long-term use has been reported to induce or exaggerate various pre-existing metabolic abnormalities including diabetes, obesity and non-alcoholic fatty liver disease (NAFLD). The mechanism(s) underlying these metabolic abnormalities is not clear; however, lipid/fatty acid accumulation due to enhanced *de novo* lipogenesis (DNL) has been shown to reduce membrane fluidity, increase oxidative stress and inflammation leading to the development of the aforementioned metabolic abnormalities. Intriguingly, emerging evidence suggest that DNL dysregulation and fatty acid accumulation could be the major mechanisms associated with the development of obesity, diabetes and NAFLD after long-term treatment with psychotropic medications in patients with PDs. In support of this, several adjunctive drugs comprising of anti-oxidants and anti-inflammatory agents, that are used in treating PDs in combination with psychotropic medications, have been shown to reduce insulin resistance and development of NAFLD. In conclusion, the above evidence suggests that DNL could be a potential pathological factor associated with various metabolic abnormalities, and a new avenue for translational research and therapeutic drug designing in PDs.

Key Words: Psychotropic medications; Metabolic complications; *De novo* lipogenesis;

Obesity; Diabetes; Non-alcoholic fatty liver disease

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Core Tip: Psychotropic medications are the first line of treatment for psychiatric disorders; however, their long-term use has been shown to induce various metabolic abnormalities including diabetes, obesity, and fatty liver disease. Although mechanism(s) underlying these metabolic abnormalities is not clear, lipid/fatty acid accumulation caused by enhanced *de novo* lipogenesis (DNL) could be the primary mediator. In this regard, various anti-inflammatory drugs that are used in combination therapy, have been shown to reduce DNL and the aforementioned metabolic abnormalities in laboratory animals. This suggests that DNL could be a potential pathological and therapeutic target, and a new avenue for translational research in psychiatric disorders.

Citation: Khan MM, Khan ZA, Khan MA. Metabolic complications of psychotropic medications in psychiatric disorders: Emerging role of *de novo* lipogenesis and therapeutic consideration. *World J Psychiatry* 2024; 14(6): 767-783

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/767.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.767>

INTRODUCTION

Although a great success has been made in understanding the pathophysiology of psychiatric disorders (PDs), therapeutic advances have not been very convincing[1-4]. While psychotropic medications including antipsychotic drugs (APs) and antidepressants (ADs) can reduce classical symptoms in patients with PDs, their long-term use has been reported to induce the development or exacerbate various pre-existing metabolic abnormalities including insulin resistance, adiposity/obesity and non-alcoholic fatty liver disease (NAFLD)[5-8]. Evidence suggests that oxidative stress and inflammation could be the major risk factors associated with various metabolic abnormalities in PDs; however, the underlying mechanisms remain(s) unclear[8-12]. Finding the underlying mechanism(s) could play a crucial role in developing effective therapies/drugs for minimizing the development of various metabolic abnormalities and improving treatment outcome and the quality of life in patients with PDs.

Over the years several mechanisms have been shown to induce oxidative stress and inflammation and associated metabolic abnormalities, they are triggered initially by the accumulation of intracellular fatty acids synthesized *via de novo* pathway/*de novo* lipogenesis (DNL)[12-19]. Although DNL produces both saturated fatty acids (SAFs) and monounsaturated fatty acids (MUFAs), evidence suggest that effect of SAFs on metabolic abnormalities could be detrimental as they increase oxidative stress and inflammation by disrupting calcium homeostasis, endoplasmic reticulum (ER) and mitochondrial function, whereas, MUFAs can induce metabolic abnormalities, specially, insulin resistance even without increasing oxidative stress and inflammation[17-21]. Since both APs and ADs have been shown to induce/deteriorate insulin resistance and other metabolic abnormalities, their effects could be most likely mediated *via* enhanced DNL.

In this review, several emerging evidence are discussed, which suggest that lipid/fatty acid accumulation caused by enhanced DNL could be the primary mechanism associated with the development of obesity, diabetes, and NAFLD during long term treatment with psychotropic medication in patients with PDs. In support of this, outcome of preliminary clinical trial studies and prospects of various adjunctive drugs/anti-inflammatory agents in reducing the development of the aforementioned metabolic abnormalities in patients with schizophrenia and depression are discussed. References cited in this review article were searched using PubMed, Scopus and Google. Only indexed articles published in English within the last five years were included. Articles published in French or German were considered only when necessary. Older articles were considered only when deemed necessary.

OVERVIEW OF PSYCHOTROPIC MEDICATIONS

Psychotropic medications are synthetic drugs/agents used in treating a wide variety of PDs including schizophrenia, psychosis, depression, bipolar disorder, mood disorder, anxiety, attention deficit hyperactivity disorder and others[22]. The most common psychotropic medications are APs, ADs, mood stabilizers, and anxiolytics or anti-anxiety drugs. However, in this review we have focused mainly on APs and ADs, their receptor binding profiles and mechanism of action are shown in Table 1.

APs

APs are the first line of treatment for schizophrenia and related psychiatric conditions. They are broadly classified into two categories; first generation or typical APs and second generation or atypical APs[23,24]. Regarding the mechanism of action, first-generation APs are designed to block dopaminergic neurotransmission, and it has been suggested that their effectiveness is optimum when they block about 72%-75% of the dopamine-2 (D2) receptors in the brain. In addition to D2

Table 1 Commonly used antipsychotic drugs and antidepressants, main mechanism of action and weight gain

Antipsychotic drugs	Main mechanism of action[23-25]	Main mechanism of action[28,29]	Weight gain[8,26,27]	Weight gain[31,32]
Typical APs				
Chlorpromazine	Blocks post-synaptic dopamine D2 receptors in the brain		+++	
Haloperidol	Blocks post-synaptic dopamine D2 receptors in the brain		+	
Thiothixene	Blocks post-synaptic dopamine D1, D2, D3, D4 receptors in the brain		+++	
Fluphenazine	Blocks post-synaptic dopamine D1 and D2 receptors in the brain		+	
Atypical APs				
Clozapine	Blocks dopamine D2 and 5HT serotonin receptors in the brain		+++	
Olanzapine	Blocks dopamine D1, D2, D3, D4 receptors, and serotonin 5HT2A, 5HT2C, 5HT3 and 5HT6, the alpha-1 adrenergic receptor		+++	
Quetiapine	Blocks dopamine D2 and serotonin 5HT2A receptors		+++	
Ziprasidone	Blocks dopamine D2 and serotonin 5HT2A receptors		-/+	
Risperidone	Blocks dopamine D2 and serotonin 5HT2A receptors		++	
Aripiprazole	Partially agonizes dopamine D2, 5-HT1A receptors, blocks serotonin 5HT2A receptors		+	
Paliperidone	Blocks dopamine D2 and serotonin 5HT2A receptors		+	
Zotepine	Blocks dopamine D1, D2 and serotonin 5HT2A, 5HT2C, 5HT6 receptors		+++	
Sertindole	Blocks dopamine D2 and serotonin 5HT2A, 5HT2C alpha-1 adrenergic receptor		+	
Amisulpride	Blocks dopamine D2 and D3 receptors		+	
Antidepressants				
SSRIs				
Sertraline		Increase serotonin 5HT level by blocking reuptake at presynaptic terminals		++
Fluoxetine				
Excitalopram				
Trazodone				
Citalopram				
Paroxetine				
SNRIs				
Duloxetine		Block serotonin and norepinephrine reuptake in the synapse, increase postsynaptic receptors' stimulation		++
Venlafaxine				
Levomilnacipran				
Atypical ADs				
Bupropion		Inhibits reuptake of dopamine and norepinephrine at the presynaptic cleft by binding to norepinephrine transporter and dopamine transporter		+

Mirtazapine	Increases release of norepinephrine into the synapse by blocking alpha-2 adrenergic receptors. Also antagonizes 5-HT receptor, increasing norepinephrine and dopamine	++
Viladozone	Enhances the release of serotonin across the brain's serotonergic pathways specifically by inhibiting the serotonin transporter	
Tricyclic ADs		
Imipramine	Increase norepinephrine and serotonin concentration by inhibiting reuptake at the presynaptic neuronal membrane	+++
Nortriptyline		
Amitriptyline		
Doxepin		
MAOIs		
Phenelzine	Increase the levels of norepinephrine, epinephrine, serotonin, and dopamine by blocking reuptake of catecholamines and serotonin at the presynaptic neuronal membrane	++
Isocarboxazie		
Tranylcypromine		

APs: Antipsychotic drugs; ADs: Antidepressants; SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin and norepinephrine reuptake inhibitors; MAOIs: Monoamine oxidase inhibitors; 5-HT: 5-hydroxytryptamine.

receptor blocking, first generation APs have been found to also block noradrenergic, cholinergic, and histamine receptors. On the other hand, second-generation APs work by blocking D2 receptors as well as serotonin (5-hydroxytryptamine) receptor. Among the various serotonin receptors, 5-HT_{2A} subtype of serotonin receptor is most commonly involved in the action of second-generation APs[23-25].

Although APs effectively reduce psychotic symptoms but, when used for extended duration, they can induce various adverse effects including sedation or dry mouth, constipation, akathisia, sexual dysfunction, acute dystonia, tardive dyskinesia, myocarditis, agranulocytosis and weight gain. Some adverse effects of APs such as hyperprolactinemia and dyslipidemia may involve long-term risk of medical complications. Although compared to the typical APs, atypical APs have been found to have the lowest propensity to cause extrapyramidal symptoms but they have highest propensity for causing weight gain and metabolic syndrome[8,26,27].

ADs

ADs are used for treating depression and major depressive disorders[22]. Over the years numerous ADs have been developed and approved by Food and Drug Administration for treating children, adults and geriatric patients with depression/major depression and various related conditions[28,29]. ADs are classified into the following groups: Selective serotonin re-uptake inhibitors (SSRIs), selective serotonin and norepinephrine re-uptake inhibitors (SNRIs), tricyclic ADs (TCAs), monoamine oxidase inhibitors and atypical ADs[28,29]. Evidence suggests that overall outcome and tolerance profile is better with the more recent ADs (SSRIs, SNRIs) than with the older agents (TCAs). Receptor binding profiles and mechanisms of action of various ADs are shown in Table 1.

Although ADs can effectively reduce symptoms of depression, their long-term use, like APs, has been shown to induce various side effects including sexual dysfunction, gastrointestinal problems, sleep disturbance, apathy, fatigue/drowsiness, insomnia, tremor, apathy and weight gain[30]. A recent meta-analysis has reported that weight gain was more prevalent in patients who received long-term treatment with TCAs[31,32]. We have discussed later the role of DNL and the mechanism associated with weight gain and other metabolic abnormalities induced by long-term treatment with both APs and ADs.

OVERVIEW OF DNL

Lipogenesis is a term used for lipid synthesis from fatty acids obtained either from the diet or synthesized *de novo* from glucose inside the cells. On the other hand, the term DNL is used for lipid synthesis from fatty acids, which are synthesized exclusively by *de novo* pathway from glucose. Excess glucose obtained from the diet or synthesized from intermediary metabolites including citrate, lactate, pyruvate, glutamate, glutamine, and glycerol can be converted into glucose and used in DNL[33-35].

In energy sufficient states or fed state, glucose is converted to pyruvate through glycolysis. Pyruvate then enters mitochondria to metabolize through Krebs cycle (tricarboxylic acid cycle) and produce citrate, which is transported back into the cytosol where it is converted to acetyl-CoA. DNL starts with ATP-dependent carboxylation of acetyl-CoA leading to the production of malonyl-CoA. In the next step, malonyl-CoA and acetyl-CoA are converted into palmitic acid (a C16 SFA) by a multi-subunit enzyme called fatty acid synthase. Palmitic acid is the predominant fatty acid synthesized during DNL. Palmitic acid can be further elongated to yield stearic acid (a C18 SFA) and also undergoes desaturation process by

the enzyme stearoyl-CoA desaturase-1 (SCD-1) to produce palmitoleic acid (C16:1 MUFA). Evidence suggest that SCD-1 can convert stearoyl-CoA to oleoyl-CoA, which is a major source for triacylglycerol (TG) synthesis. Palmitic acid and stearic acid can be further elongated and desaturated to give higher MUFAs including nervonic acid as the terminal product[33-35]. Although under normal physiological conditions DNL is a tightly regulated process, enhanced DNL has been associated with various metabolic diseases[35], which could be a likely scenario in patients with PDs treated with psychotropic medications[12].

PSYCHOTROPIC MEDICATIONS ENHANCE DNL

Over the years several studies have shown that membrane lipid/fatty acid abnormalities are strongly associated with cognitive and classical symptoms in patients with PDs[36-39]. Although most of these studies have focused mainly on polyunsaturated fatty acids (PUFAs), little or no attention is given to the role of SAFs and MUFAs, which are supplied mainly by DNL. Evidence suggests that DNL is essential for brain and peripheral tissue development and metabolic homeostasis[40-43]. However, enhanced DNL has been associated with inflammation and various metabolic abnormalities including insulin resistance/diabetes, obesity, and NAFLD[12,13,34,35,44-48]. Since psychotropic medications have been shown to induce or exaggerate these metabolic abnormalities, enhanced DNL could be a major mediator.

Red blood cells (RBCs) membrane fatty acids (SAFs and MUFAs) have been used to measure the extent of DNL in health and disease including PDs[46,49-51]. In schizophrenia, we reported long back that the levels of RBC's SFAs, MUFAs, and PUFAs were significantly elevated in patients with psychosis treated with APs compared to the untreated patients and control subjects (Figure 1 and Table 2)[36]. A number of other studies including those conducted in recent years have also reported similar changes in the levels of SFAs, MUFAs, and PUFAs in the RBC membrane from patients with psychosis after treatment with APs[37-39,42,52,53]. In addition to RBCs fatty acids, plasma free fatty acids and TG levels have also been found to be significantly increased after treatment with APs[54-56]. Changes in membrane fatty acids and TGs seem to be the result of enhanced DNL, and not due to binge eating or other confounders because; they showed strong association with cognitive and clinical symptom scores[37-39,57].

In depression, several studies have reported increase in the RBC's fatty acid contents after treatment with various ADs [58-61]. Evidence suggests that treatment with ADs can also increase plasma as well as hepatic TGs most likely by increasing DNL[62]. Further, changes in various fatty acids and TG levels were strongly associated with clinical symptoms scores in patients with depression[59-62]. Altogether, the above evidence suggests that treatment with both APs and ADs can increase the levels of both SFAs and MUFAs *via* increasing DNL in patients with PDs. This could be a potential risk factor associated with various metabolic abnormalities including insulin resistance/diabetes, obesity and NAFLD induced by long-term treatment with psychotropic medications.

PSYCHOTROPIC MEDICATIONS INDUCE DIABETES

Evidence suggests that under normal physiological condition, insulin regulate both gluconeogenesis and DNL, whereas, insulin resistance stimulates gluconeogenesis and DNL[47,63]. It has been reported in humans that the level of SAFs of DNL in adipose tissue is negatively associated with insulin sensitivity[64]. Thus, elevated SFAs along with MUFAs synthesized *via* DNL could be the major players involved in insulin resistance in patients with PDs.

Although evidence suggest that insulin resistance could be developed from the early stage of the illness in patients with PDs, treatment with psychotropic medications may further deteriorate insulin resistance[65-68]. In drug-naïve patients with early psychosis, Steiner *et al*[69] assessed homeostatic model assessment of insulin resistance (HOMA-IR) and stress hormone levels, and found that insulin resistance and disrupted glucose homeostasis could be illness related and not due to pharmacotherapy, adiposity, or hormonal stress axis activation; although, levels of serum stress hormone may be increased. In another study, Chouinard *et al*[68] studied insulin resistance in patients with first-episode psychosis and suggested that abnormal glucose metabolism could be related to risk for psychosis, independent of disease expression and treatment effects. Pillinger *et al*[70] performed a meta-analysis and noticed elevated HOMA-IR in drug-naïve patients with first-episode compared with controls. Thus, while the above evidence suggest that insulin resistance may develop from the early stage of the illness in patients with PDs, recent studies have reported that treatment with APs further deteriorate insulin resistance, which could be aligned with the increase in body weight[71,72].

Likewise, in depression several studies have shown that insulin resistance could be present in a significantly high proportion of patients before the diagnosis of classical symptoms, and it may either remain unchanged or deteriorate further leading to the development of diabetes and obesity after long-term treatment with ADs[65,67,73,74]. Although, there may be some controversies, a recent meta-analysis has reported that risk of insulin resistance is also increased even in children and adolescence after treatment with ADs[75]. Altogether, the above evidence suggests that insulin resistance could be an intrinsic risk factor, which may deteriorate further triggering the development of obesity and NAFLD following treatment with psychotropic medications.

Table 2 Effect of psychotropic medications on the markers of *de novo* lipogenesis, gluconeogenesis and metabolic abnormalities in patients with psychiatric disorders

Parameters	Antipsychotic drugs	Antidepressants
<i>De novo</i> lipogenesis (markers)		
SFAs	Increased[36,39]	Increased[58,61]
MUFAs	Increased[36,39]	Increased[58,61]
PUFAs ¹	Increased[36,39]	Increased[58,61]
Gluconeogenesis (precursors)		
Lactate	Increased[125,126]	Decreased[128]
Citrate	Increased[129]	?
Pyruvate	Increased[129]	Increased[128]
Glutamate	Increased[129,130]	Increased[128]
Metabolic abnormalities		
Blood glucose	Increased[72,121]	Increased[122,131]
IR/insulin level ²	Increased[55,133]	Increased[65,74,75]
Triglycerides	Increased[8,55,56,72]	Increased[122]
Obesity (BMI)	Increased[8,55,72]	Increased[31,32,122]
Leptin	Increased[57,87]	Increased[132]
Adiponectin	Increased[55,89]	No change[65,134]
Resistin	Increased[55,89]	Reduced[134]
Diabetes	Increased[8,55,72]	Increased[5,65,74,135]
NAFLD	Increased[7,97,123]	Increase[95,96]

¹Polyunsaturated fatty acids are obtained through the diet, they are not synthesized *via de novo* lipogenesis in the body.

²Insulin resistance is a positively and strongly associated with *de novo* lipogenesis.

SFAs: Saturated fatty acids; MUFAs: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids; IR: Insulin resistance; BMI: Body mass index; NAFLD: Non-alcoholic fatty liver disease.

PSYCHOTROPIC MEDICATIONS INCREASE ADIPOSITY/OBESITY

Although patients with PDs may have elevated risk for adipose tissue dysfunction from the early stage of illness, obesity usually develops or become more severe after treatment with psychotropic medication[72,73,76,77]. Adipose tissue is one of the two major sites for DNL under normal conditions, evidence suggests that adipose tissue DNL could be enhanced in patients with PDs[12,55,57,60,61,67]. Although adipocytes can synthesize and store excess lipids/fats without being inflammatory, insulin resistance has been associated with adipocyte hypertrophy and secretion of pro-inflammatory cytokines[78-80]. In addition, hypersensitized adipocytes can release SAFs and MUFAs into circulation, which can lead to the activation and transformation of circulating monocytes into macrophages[81,82]. Intriguingly, several evidence suggest that monocytes could be activated and associated with increased macrophage activation and inflammation in patients with PDs[83,84]. Activated macrophages, in turn, can accumulate SAFs *via* enhanced DNL and secrete various pro-inflammatory cytokines in adipose tissue; some of these cytokines such as tumor necrosis factor (TNF)- α , can activate nearby adipocytes leading to the formation of a paracrine inflammatory loop between macrophages and adipocytes[14,15,81,82]. Evidence suggests that formation of inflammatory loop between adipocytes and macrophages can result in hypersensitization of adipose tissue leading to irreversible increase in body weight and insulin resistance[81,82].

Adipocyte-macrophage inflammatory cascade, involving activated monocytes, could be the primary mediator of adipose tissue abnormalities induced by long-term treatment with psychotropic medications in patients with PDs[55,77,84,85]. In support of this, several studies including our own, have shown that membrane SFAs, fasting glucose, C-reactive protein, and adipokines including adiponectin and resistin are increased but leptin is decreased in patients with recent onset PDs[28,39,57,86-89]. Evidence suggests that while all fatty acids can inhibit adipokine/leptin production, effect of SAFs could be detrimental[12,57,89,90]. In addition, elevated SAFs in adipocytes and intercalated macrophages can stimulate *de novo* biosynthesis of ceramides, which can further potentiate inflammatory effect of SFAs in adipose tissue by disrupting adipokine secretion and signaling in patients with PDs[21,86,91,92]. Moreover, adipose tissue abnormalities are directly associated with cardio-vascular dysfunctions in obese individuals; therefore, cardio-vascular dysfunction in patients with PDs could be influenced by both impaired membrane fluidity of vascular endothelial cells as well as adipose tissue abnormalities most likely induced by elevated SFAs synthesized *via* DNL[53,55,93].

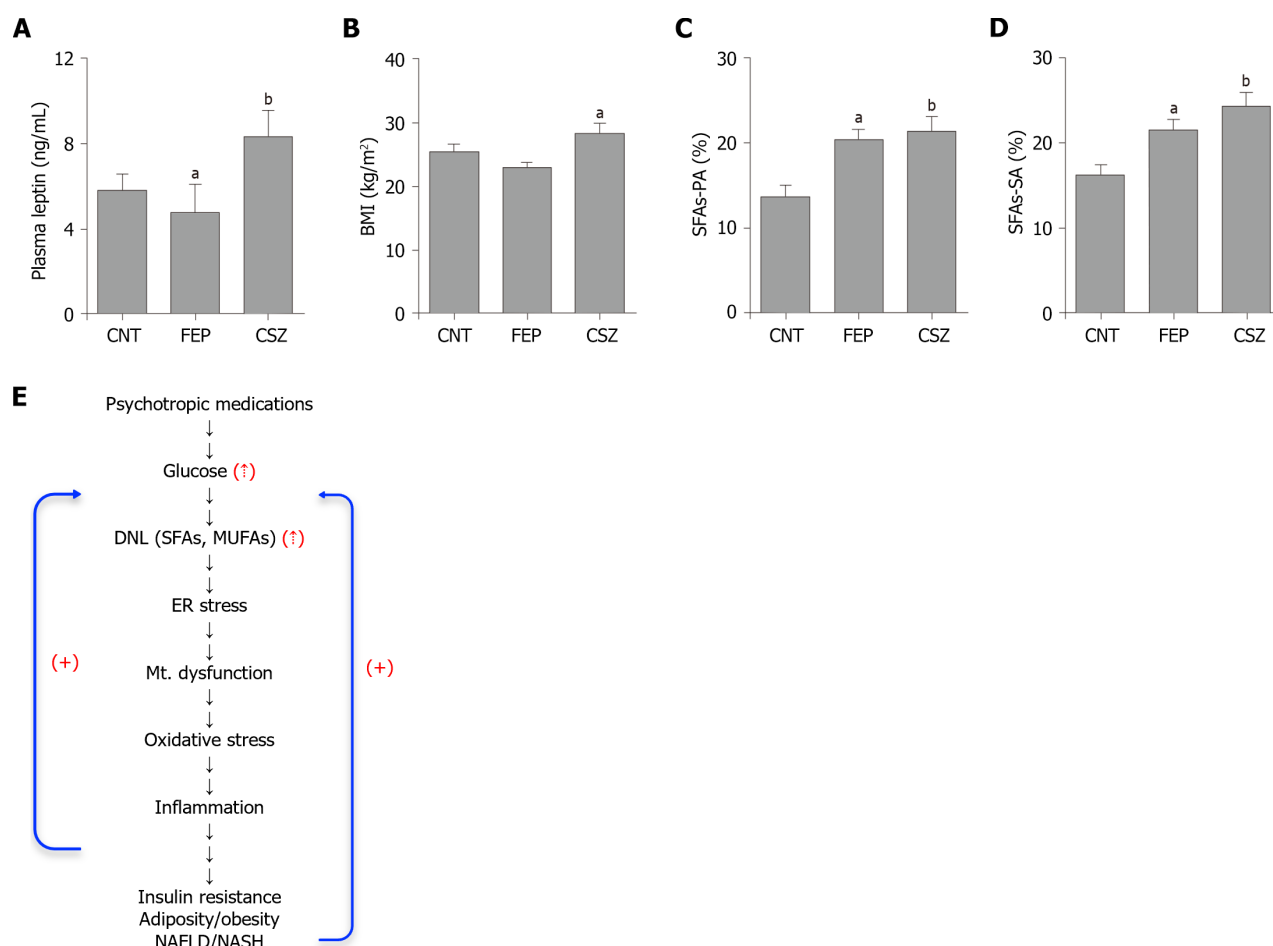


Figure 1 Influence of antipsychotic drugs on metabolic parameters. A: Plasma leptin in control subjects, drug-naïve first-episode and antipsychotic-treated chronic schizophrenia patients; B: Body mass index; C: Saturated fatty acids (SAFs)-palmitic acid; D: SFAs-stearic acid in the same groups; E: Psychotropic medications increase stimulate SAFs and monounsaturated fatty acids levels by increasing *de novo* lipogenesis. SFAs can induce endoplasmic reticulum stress, mitochondrial dysfunction and development of various metabolic abnormalities including insulin resistance, adiposity/obesity, and non-alcoholic fatty liver disease/steatohepatitis. Red arrows indicate increase, and blue arrows indicate stimulatory (+) effect of oxidative stress and inflammation on *de novo* lipogenesis and various metabolic abnormalities. CNT: Control; FEP: First-episode; CSZ: Chronic schizophrenia; BMI: Body mass index; SFAs-PA: Saturated fatty acids-palmitic acid; SFAs-SA: Saturated fatty acids-stearic acid; SFAs: Saturated fatty acids; MUFAs: Monounsaturated fatty acids; ER: Endoplasmic reticulum; DNL: *De novo* lipogenesis; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; Mt: Mitochondrial. Citation for Figure A-D: Khan MM. Disrupted leptin-fatty acid biosynthesis is an early manifestation of metabolic abnormalities in schizophrenia. *World J Psychiatry* 2022; 12: 827-842. Copyright© The Authors 2022. Published by Baishideng publishing Group. It is open access and permits to use materials provided it's been cited properly.

PSYCHOTROPIC MEDICATIONS TRIGGER THE DEVELOPMENT OF NAFLD

Over the years several authors have investigated the prevalence of liver disease before and after treatment with psychotropic medications in patients with PDs. The available data suggests that a great majority of patients with PDs possess pre-existing risk of developing NAFLD/non-alcoholic steatohepatitis (NASH) within 1-3 years following treatment with psychotropic medications[7,94-96]. Epidemiological studies have shown that extent of NAFLD/NASH prevalence may vary from 27% in United States to as high as 50% in China in patients with PDs compared to the general population. And evidence suggest that the onset of NAFLD/NASH could be positively associated with circulating triglycerides, body mass index, combination and dosage of psychotropic medications, and clinical symptoms in PDs[94-97].

Liver inflammation/NAFLD, irrespective of the cause, is triggered by the dysregulation of DNL leading to lipid/fatty acid accumulation within the hepatocytes[45]. In PDs, whether increased prevalence of NAFLD/NASH is associated with enhanced DNL remains to be validated. However, recent studies have shown that increased plasma and liver free fatty acids and TGs in normal population with NAFLD/NASH are primarily a result of enhanced DNL in liver. Since treatment with both APs and ADs increases plasma free fatty acid, TGs, and the risk of NAFLD/NASH; therefore, enhanced DNL could be a major risk factor associated with the development of NAFLD/NASH in patients with PDs[7,45, 95,96,98,99].

As discussed before, several lines of evidence suggest that insulin resistance could be a potential risk factor for developing PDs[66]. Insulin resistance also strongly stimulates hepatic DNL leading to lipid/fatty acid accumulation and development of NAFLD/NASH[37,68,100]. Since, insulin resistance may develop from the early childhood age in patients with PDs, as a consequence, DNL could also be enhanced coinciding with the development of insulin resistance [66]. Although increased SFAs, synthesized *via* DNL, can activate several pro-inflammatory pathways associated with

insulin resistance, they can also be incorporated into membrane phospholipids resulting into reduced membrane fluidity, which can further potentiate inflammatory response and hepatic insulin resistance and progression to NAFLD/NASH, and this could be a likely scenario after treatment with psychotropic medications in patients with PDs. Further, evidence suggest that excess SFAs and TGs produced by liver DNL could be released in circulation, and can activate adipocytes and blood immune cells, specially, monocytes leading to further potentiation of pro-inflammatory cues in patients with PDs[45,98,100,101].

MECHANISM(S) OF PSYCHOTROPIC MEDICATION-INDUCED ADIPOSITY/OBESITY AND NAFLD

Regarding the mechanism(s) associated with the development of various metabolic abnormalities by psychotropic medications, elevated fatty acids/lipids (SFAs, MUFAs, TG) and leptin together can activated/alter multiple signaling pathways involved in oxidative stress, inflammation and development of various metabolic abnormalities in PDs[12,18,19,59]. Although it is not clear how psychotropic medications increase fatty acid/lipid and leptin synthesis, disruption of calcium homeostasis/signaling could be the major causative factors because; both APs and ADs have been shown to block/inhibit various voltage-gated and non-voltage gated calcium channels, and calcium supplementation has been shown to significantly reverse the early weaning-induced metabolic abnormalities including hyperleptinemia in adult animals[102-106]. Also, several studies have shown that calcium supplementation reduces plasma leptin production (increased leptin production beyond physiological limit is positively associated with obesity), and development of obesity and NAFLD in obese individuals and laboratory animals[106-109]. Thus, while the above findings suggest that psychotropic medications may increase leptin synthesis, body weight and the extent of NAFLD in patients with PDs, it could be a result of perturbed calcium signaling/availability.

An overwhelming body of evidence suggests that elevated SFAs can disrupt insulin signaling and energy homeostasis by altering ER and mitochondrial function (Figure 1). Cell culture studies have shown that treatment with SFAs causes abrupt release of Ca^{2+} from ER thereby depleting ER Ca^{2+} store. This leads to a sharp increase in cytosolic and mitochondrial Ca^{2+} concentration mediated by store-operated Ca^{2+} channels[19]. This process has been shown to increase reactive oxygen species formation as a consequence of ER stress and mitochondrial dysfunction (Figure 1). Further, several studies have shown that SFAs, particularly, palmitic acid can induce ER stress in a variety of distantly related cells and tissues including pancreas, adipose tissue, and brain by altering Ca^{2+} homeostasis[19].

It has been shown that SFAs-induced activated adipocytes as well as macrophages, mainly, inflammatory type (M1 type) play a major role in inflammation by producing several pro-inflammatory cytokines including interleukin (IL)-1b, IL-6, IL-8, and TNF- α [19]. Since SFAs have been shown to increase these pro-inflammatory markers, and SFAs are further increased after treatment with psychotropic medications, which therefore could be a major contributing factor in the development of pro-inflammatory response and metabolic abnormalities during long-term treatment with psychotropic medication in patients with PDs[36,58-61].

Several lines of evidence suggest that elevated leptin can induce adiposity/fat mass accumulation. It has been shown to potentiate inflammatory, lipogenic, and adipogenic response in cellular and animal models[110-112]. Leptin treatment of adipocytes has been shown to increase the synthesis of various inflammatory cytokines including TNF- α , IL-10, and IL-6 [110]. Evidence suggest that together with TNF- α , leptin can activate macrophages leading to increased secretion of inflammatory cytokines, which may further amplify inflammatory response[113-115]. Also, leptin either alone or in association with TNF- α can induce inflammation of the pancreas disrupting β -cell function and insulin secretion[110,116,117], a scenario typically seen in patients with PDs after long-term treatment with psychotropic medications.

Adipogenic effect of leptin could be enhanced further by increased DNL and adiposity/obesity[110]. It has been shown that leptin can increase the production of PLIN1, CAV-1, PPAR γ , SREBP1C, and/or adiponectin[110]. These proteins together increase transcription of various genes involved in adipocyte differentiation. Regarding the signaling pathways involved in lipogenic effect, evidence suggest that leptin can increase lipid accumulation in adipocytes *via* mechanistic target of rapamycin-dependent pathway[110], which may occur even without insulin action that is crucial for pre-adipocyte differentiation. These findings suggest that leptin may stimulate adipocyte differentiation and DNL even in the absence of insulin signaling. In support of this, it has been shown recently that removing circulating plasma leptin can reduce body weight and hyperglycemia in obese rats[112]. This is an interesting outcome, which may lead to designing leptin-based treatment for reducing obesity and diabetes develop during long-term treatment with psychotropic medications.

Regarding the role of leptin in the development of NAFLD, elevated leptin has been associated with the increased risk of NAFLD. In one study, analysis of 4571 patients with NAFLD, leptin level progressively increased with the increase in the severity of NAFLD[118]. Although, some report suggests that higher leptin level may be protective against NAFLD, result of recent meta-analyses suggest that elevated leptin could be a potential risk factor for developing NAFLD[119,120]. Moreover, since leptin elevation is strongly associated with obesity, and obesity is positive associated with NAFLD; therefore, it can be hypothesized that hyperleptinemia in obese individuals may accelerate the development of NAFLD, a scenario that most likely develops during long-term treatment with psychotropic medication in patients with PDs.

CLINICAL IMPACT AND THERAPEUTIC CONSIDERATIONS

Although psychotropic medications are the first line of treatment for PDs, as discussed above that their long-term use can induce or exacerbate various metabolic abnormalities including insulin resistance/diabetes, obesity, and NAFLD[7,8,72-

Table 3 Effect of selective adjunctive/anti-inflammatory drugs on symptoms of psychosis, depression, insulin resistance and non-alcoholic fatty liver disease

Agents/drugs	Psychosis ¹	Depression ²	Insulin resistance ³	NAFLD ⁴
Aspirin	Reduced[136,137]	Reduced[142]	Reduced[151]	Reduced[160]
N-acetylcysteine	Reduced[136,137]	Reduced[143]	Reduced[152]	Reduced[161]
Minocycline	Reduced[136,137]	No change[144]	Reduced[153]	Increased[162]
Pregnenolone	Reduced[137]	Reduced[145]	?	Reduced[163]
Estrogens	Reduced[136,137]	Reduced[146]	Reduced[154]	Reduced[164]
Raloxifene	Reduced[137]	?	May reduce[155]	Reduced[165]
Curcumin	Reduced[138]	Reduced[147]	Reduced[156]	Reduced[166]
Pioglitazone	Reduced[139]	Reduced[148]	Reduced[157]	Reduced[167]
Celecoxib	Reduced[140]	Reduced[149]	Reduced[158]	Reduced[168]
w3-PUFAs	Reduced[141]	Reduced[150]	Reduced[159]	Reduced[169]

¹Measure of positive and negative syndrome scale score.

²Measure of Hamilton depression rating scale total scores.

³Measure of insulin resistance and hyperglycemia.

⁴Non-alcoholic fatty liver disease is positively associated with *de novo* lipogenesis; thus, reduced non-alcoholic fatty liver disease indicates a decrease in *de novo* lipogenesis.

NAFLD: Non-alcoholic fatty liver diseases; w3-PUFAs: w-3 polyunsaturated fatty acids.

75,95,96,121-123]. Even early intervention with psychotropic medications has been shown to trigger the development of various metabolic abnormalities in children and adolescents with PDs[124,125]. The mechanism(s) underlying these metabolic abnormalities remains to be documented; however, as discussed before that DNL dysregulation leading to fatty acid accumulation could be the likely mechanisms involved[7,12,57]. In support of this, several studies have shown that the levels of RBC's SFAs and MUFAs are increased in patients with PDs after treatment with psychotropic medications compared to the untreated patients or control subjects[36,39,58,61]. Since RBC's fatty acid (SAFs and MUFAs) composition can be used to assess the extent of DNL in health and diseases, increased RBC's SAF and MUFA levels by treatment with psychotropic medications suggest that DNL could be enhanced[12,46,51,57]. In support of this, several intermediary metabolites used in DNL including lactate, pyruvate, glutamate and glutamine among others are increased after treatment with psychotropic medications[126-135] (Table 2). Thus, while these evidences suggest that targeting DNL could be an effective strategy for minimizing the risk of developing/exacerbating various metabolic abnormalities following long-term treatment with psychotropic medications, data from preliminary clinical trial studies conducted with various adjunctive drugs that reduce NAFLD/NASH strongly support this notion (Table 3).

In the last two decades, several combination therapy trials have been conducted with adjunctive drugs including anti-inflammatory agents and anti-oxidants in PDs[136-139]. Addition of these adjunctive drugs to the clinically approved doses of APs or ADs have been shown to reduce symptoms of psychosis and depression (Table 3). While these agents also reduce insulin resistance, evidence suggests that this effect could be a result of reduced DNL as evident by decrease in NAFLD/NAD (Table 3). Among these agents, aspirin, minocycline, N-acetylcysteine, pregnanolone, estrogen, raloxifene (estrogen receptor modulators), and curcumin have been found to reduce NAFLD/DNL in various experimental studies (Table 3). Development of NAFLD can affect multiple systems and is associated with various metabolic abnormalities including dyslipidemia, insulin resistance, obesity, and cardiovascular diseases and is triggered primarily by dysregulated DNL[50,170,171].

As shown in Table 3, that most of the adjunctive drugs, mentioned above, have been shown to reduce NAFLD in various experimental studies. These findings, together with the favorable effects of these drugs on symptoms of depression and psychosis suggest that enhanced DNL could be an intrinsic risk factor associated with the etiopathology of PDs. Therefore, large randomized clinical trials with therapeutic agents that inhibit/regulate DNL are warranted. In this context, excellent recent reviews by Batchuluun *et al*[34], and Jeon *et al*[35] which have presented a detailed account of functional and clinical significance of various DNL inhibitors, can be considered.

Since the evidence discussed earlier suggests that enhanced DNL could be the primary mediator of insulin resistance, which may develop from the early childhood age in patients with PDs; therefore, early intervention with appropriate therapeutic agents that regulate/inhibit DNL may reverse/normalize cellular signaling(s) that leads to the development of brain and peripheral tissue inflammation, and various metabolic abnormalities in patients with PDs. For early intervention, some adjunctive drugs, namely, N-acetylcysteine, pioglitazone or curcumin can be given preference over others[12]. N-acetylcysteine has been shown to reduce most of the psychotic symptoms, inflammation, insulin resistance and NAFLD, while having positive effect on cognition and neurogenesis (Table 3). Although, estrogen has been found effective in reducing psychosis, possible induction of feminization effect limits its extensive use in men. On the other hand, raloxifene, a synthetic selective estrogen receptor modulator that does not carry the risk of feminization, and

therefore, could be effective both in young men and women with schizophrenia. However, its effectiveness in patients with depression remains to be documented (Table 3). In addition to these agents, curcumin has been shown to reduce inflammation, insulin resistance, and NAFLD while significantly reducing symptoms of depression and psychosis in patients with PDs [138,147,156,166]. These findings together with profound influence of curcumin on neurogenesis and cognition in young and aged rats suggest that it could be worthy of further large-scale clinical trials in patients with PDs [172,173].

CONCLUSION

The evidence discussed above suggests that insulin resistance may develop from the early childhood age in patients with PDs. Since insulin resistance is positively associated with DNL; therefore, DNL could also be enhanced from the early childhood age in patients with PDs. Although elevated intracellular fatty acids (SAFs and MUFAs) synthesized *via* DNL could be the primary mediators of insulin resistance, both insulin resistance and DNL are further deteriorated after treatment with psychotropic medication leading to the development of obesity and NAFLD. This suggests that DNL could be a potential pathological factor associated with various metabolic abnormalities and, targeting DNL could be an effective strategy for reducing the deterioration or development of these metabolic abnormalities and improving global outcome in patients with PDs after treatment with psychotropic medications.

While clinical trial(s) with specific DNL inhibitor(s) have not been performed, various adjunctive drugs used in combination with psychotropic medications in treating patients with PDs have been shown to reduce the development of insulin resistance and NAFLD in laboratory animals (Table 3). Some of these adjunctive drugs, namely, N-acetylcysteine, pioglitazone and curcumin have satisfactory safety profiles and are therefore worthy of early intervention and long-term use in PDs. Regarding the early intervention, since insulin resistance is potential a risk factor for developing PDs and could be diagnosed during childhood stage or before the onset of classical symptoms in patients with PDs; therefore, early intervention with an appropriate adjunctive drugs or other therapeutic agents that reduced/regulate DNL and insulin resistance may normalize cellular signaling/mechanism, which leads to the development of various metabolic abnormalities in patients with PDs.

ACKNOWLEDGEMENTS

We sincerely acknowledge the facilities provided by the Department of Biotechnology, Era's Lucknow Medical College and Hospital, and Faculty of Science, Era University, Lucknow, India.

FOOTNOTES

Author contributions: Khan MM conceptualised the idea and wrote the manuscript; Khan ZA and Khan MA provided the resources.

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

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L-Editor: A

P-Editor: Chen YX

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Case Control Study

Cognitive dysfunction in schizophrenia patients caused by down-regulation of γ -aminobutyric acid receptor subunits

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Harnett NG, United States

Received: March 7, 2024

Revised: April 25, 2024

Accepted: May 10, 2024

Published online: June 19, 2024

Processing time: 104 Days and 4.2 Hours



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Abstract

BACKGROUND

The expression pattern of gamma aminobutyric acid (GABA) receptor subunits are commonly altered in patients with schizophrenia, which may lead to nerve excitation/inhibition problems, affecting cognition, emotion, and behavior.

AIM

To explore GABA receptor expression and its relationship with schizophrenia and to provide insights into more effective treatments.

METHODS

This case-control study enrolled 126 patients with schizophrenia treated at our hospital and 126 healthy volunteers who underwent physical examinations at our hospital during the same period. The expression levels of the GABA receptor subunits were detected using ¹H-magnetic resonance spectroscopy. The recognized cognitive battery tool, the MATRICS Consensus Cognitive Battery, was used to evaluate the scores for various dimensions of cognitive function. The correlation between GABA receptor subunit downregulation and schizophrenia was also analyzed.

RESULTS

Significant differences in GABA receptor subunit levels were found between the case and control groups ($P < 0.05$). A significant difference was also found between the case and control groups in terms of cognitive function measures, including attention/alertness and learning ability ($P < 0.05$). Specifically, as the expression levels of GABRA1 ($\alpha 1$ subunit gene), GABRB2 ($\beta 2$ subunit gene), GABRD (δ subunit), and GABRE (ϵ subunit) decreased, the severity of the patients' condition increased gradually, indicating a positive correlation between the downregulation of these 4 receptor subunits and schizophrenia ($P < 0.05$). However, the expression levels of GABRA5 ($\alpha 5$ subunit gene) and GABRA6 ($\alpha 6$ subunit gene) showed no significant correlation with schizophrenia ($P > 0.05$).

CONCLUSION

Downregulation of the GABA receptor subunits is positively correlated with schizophrenia. In other words, when GABA receptor subunits are downregulated in patients, cognitive impairment becomes more severe.

Key Words: Cognitive function; Schizophrenia; Downregulation; Gamma-aminobutyric acid receptor subunits; Correlation

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Core Tip: The levels of gamma-aminobutyric acid (GABA) receptor subunits differ between the brains of patients with schizophrenia and those of healthy individuals. Patients with schizophrenia show cognitive impairments due to problems with attention, memory, social cognition, and executive functions. Furthermore, downregulation of the GABA receptor subunits GABRA1, GABRB1, GABRD, and GABRE is positively correlated with declining cognitive function in schizophrenia patients. No significant correlation was found between the subunit expression levels of GABRA5 and GABRA6.

Citation: Chen X, Zhou YN, Lu XZ, Li RJ, Xiong YF, Sheng X, Zhu WW. Cognitive dysfunction in schizophrenia patients caused by down-regulation of γ -aminobutyric acid receptor subunits. *World J Psychiatry* 2024; 14(6): 784-793

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/784.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.784>

INTRODUCTION

Schizophrenia is a complex and devastating genetic psychiatric disorder worldwide, with high relapse and disability rates and a lifelong prevalence of 1% [1]. It is primarily characterized by disturbances in perception, thought, emotion, and behavior, with discoordination between the environment and mental activities [2]. It often begins in early adulthood, showing a slow and protracted course [3]. Some patients may experience a cognitive decline, which not only causes great suffering to the patients and their families, but also imposes a heavy economic burden on society.

Schizophrenia has complex clinical features, including positive (delusions, hallucinations, and thought disorders) and negative symptoms (blunted affect and social withdrawal) [4]. Cognitive impairment, including attention, working memory, executive function, and social cognition, is a core symptom that includes both the psychological and social aspects of cognition [5]. There is a strong correlation between cognitive impairment and long-term outcomes in patients with schizophrenia, as cognitive impairment appears before other psychiatric symptoms [6]. Therefore, cognitive function can be used to predict disease progression and treatment response to treatment [7]. In recent years, patients with cognitive impairment have received increasing attention.

Gamma aminobutyric acid (GABA) is a primary inhibitory neurotransmitter [8], found in approximately 50% of central synapses, which plays an important role in controlling neuronal excitability [9]. In addition to its distribution in various parts of the brain, GABA is associated with a variety of higher brain functions such as attention, working memory, emotions, and motor inhibition. The hypothesis of GABA deficiency in schizophrenia has been established over the past 30 years [10]. In 1972, Roberts proposed, for the first time, a correlation between schizophrenia and GABA system deficiency through his study on the interaction between GABA and DA in the basal ganglia [11]. Based on this, other researchers have established a theory of the interactions between GABA and dopamine in the striatum and marginal system, suggesting a weakened inhibitory effect of GABA on dopamine activity, leading to abnormal behavior [12]. Numerous studies have implicated the GABAergic neurotransmitter system in the pathogenesis of schizophrenia, according to numerous studies [13].

The association between GABA receptor gene clusters and schizophrenia has become a popular research topic in recent years [14]. Currently, several genes related to the GABA hypothesis of schizophrenia have received increasing attention, including GABRA1 ($\alpha 1$ subunit gene), GABRB2 ($\beta 2$ subunit gene), GABRA5 ($\alpha 5$ subunit gene), GABRA6 ($\alpha 6$ subunit gene), GABRD (δ subunit), and GABRE (ϵ subunit) [15-17]. This study aimed to investigate the relationship between schizophrenia and the downregulation of GABA receptor subunits and to analyze how GABA receptor subunit expression levels correlate with schizophrenia symptoms and severity.

MATERIALS AND METHODS

General information

Data from 196 patients with schizophrenia who were admitted in our hospital from March 2022 to August 2023 were collected retrospectively. A total of 126 patients were selected as the case group based on the inclusion and exclusion criteria, while 126 healthy volunteers matched for age, sex, and education level, who underwent physical examination at our hospital in the same time period were randomly selected as the healthy control group. Data on age, sex, body mass index (BMI), education, living environment, type of schizophrenia, Brief Psychiatric Rating Scale (BPRS) score, smoking history, drinking history, and complications were collected for both groups.

Inclusion and exclusion criteria

The inclusion criteria for schizophrenia patients were[18]: (1) Patients diagnosed with schizophrenia in accordance with the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders[19]; (2) Age 18-50 years, with no abnormalities in a routine blood examination; and (3) The main type of schizophrenia was the paranoid type. Exclusion criteria were as follows: (1) Patients with diabetes, thyroid disease, hypertension, cardiovascular disease, or other diseases that could adversely affect their microbiota; (2) Recent diarrhea and pregnancy or breastfeeding; and (3) Over one month of olanzapine, aripiprazole, quetiapine, and haloperidol administration.

The inclusion criteria for healthy controls were as follows: (1) No mental illness; (2) 18-50 years old; and (3) Primary school education or above, able to understand the research content. The exclusion criteria were: (1) Mental retardation or other serious mental disorders; (2) Organic brain or other serious somatic diseases; (3) History of drug or alcohol abuse; and (4) Mental retardation.

Detection of GABA receptor subunit levels

Blood samples were collected from patients with schizophrenia and healthy controls to determine the expression levels of GABA receptor subunits. The expression levels of GABA receptor subunits were detected using 1H-magnetic resonance spectroscopy (1H-MRS), at each visit, using the same 1H-MRS pulse sequences and equipment. By comparing the differences in GABA receptor subunit expression levels between patients with schizophrenia and healthy controls, further analyses were conducted to determine their relevance to schizophrenia. Additionally, the relationship between GABA receptor subunit expression levels and disease progression was analyzed based on the severity of patients' symptoms.

Cognitive function scores

The first step in assessing the cognitive function scores was to determine whether patients were conscious. The severity of consciousness impairment was evaluated using the MATRICS Consensus Cognitive Battery (MCCB). MCCB Data Quality Assurance was assured by ensuring that each tester who interacted with the patients was trained in the administration and scoring of the MCCB through video and group sessions. If the patient was conscious, cognitive dysfunction was assessed using the BPRS[20]. Examination results can be used to determine whether patients have cognitive dysfunction and to further assess their cognitive function.

Statistical analysis

Statistical software (SPSS 26.0) was used to analyze the data. Continuous data is represented as the mean \pm SD, and comparisons were conducted using the *t*-test. Categorical data is represented in the form of [*n* (%)], and comparisons were made using the χ^2 test. Statistical significance was set at $P < 0.05$.

RESULTS

Comparison of baseline data results

As shown in Table 1, both the case and control groups were demographically and clinically similar. Baseline data, including age, sex, BMI, living environment, comorbidities, and years of education, did not show statistically significant differences ($P > 0.05$) between the two groups. A flowchart of the study is shown in Figure 1.

Comparison of GABA receptor subunit expression levels

As shown in Table 2, in contrast to healthy controls, patients with schizophrenia showed downregulated expression of GABA receptor subunits, which correlated with the risk of schizophrenia. In schizophrenia patients, GABRA1, GABRB2, GABRD, and GABRE expression levels were significantly lower than those in the healthy control group ($P < 0.05$), whereas the expression levels of the GABRA5 and GABRA6 subunits were not significantly different from those in the healthy control group ($P > 0.05$).

Comparison of cognitive scores

Figure 2 shows a comparison of cognitive scores between the two groups. The case group scored significantly lower than the healthy control group ($P < 0.001$) in all four cognitive domains. The ability to process information quickly, maintain working memory, learn words, and solve problems is a part of the cognitive process. A significant difference was observed between the two groups in the visual learning domain of visual learning ($P = 0.026$). However, there were no significant differences in the attention/alertness domains ($P = 0.73$).

Table 1 Comparison of general data of two groups

Index	Case group (n = 126)	Control group (n = 126)	χ^2/t	P value
Age (yr)	35.32 ± 4.81	36.75 ± 4.96	1.311	0.162
Sex (n)				
Male	56	59	1.035	0.291
Female	70	67		
BMI (kg/m ²)	23.50 ± 3.12	23.36 ± 3.15	0.675	1.503
Education level			0.096	9.721
Illiterate	16	18		
Primary school	26	23		
Junior high school	49	51		
High school and above	35	34		
Living environment			0.853	0.352
In the city	65	64		
In the countryside	61	62		
The types of schizophrenia				
Paranoid type	126	-		
BPRS scores			0.263	0.639
Positive symptoms	-	16.19 ± 3.82		
Negative symptoms	-	8.35 ± 2.39		
Total BPRS scores	-	46.61 ± 4.53		
Drinking			1.132	0.214
Yes	62	61		
No	64	65		
Smoking history			1.344	0.202
Yes	55	52		
No	71	74		
Complications			0.228	0.893
Diabetes	43	45	0.753	0.372
Hypertension	56	52		

BMI: Body mass index; BPRS: Brief Psychiatric Rating Scale.

Correlation analysis between downregulation of GABA receptor subunits and cognitive behavior in patients with schizophrenia

In this study, we examined the correlation between four GABA receptor subunits, with significant differences between the two groups of patients, and six cognitive domains of the MCCB (ability to process information efficiently, be attentive, maintain working memory, learn words, acquire visual perception, reason, and solve problems). In healthy controls, there was no correlation between the downregulation of GABA receptor subunits and cognitive function ($P > 0.05$).

Correlation analysis of GABA receiver subunit downregulation and information processing speed

Table 3 shows a positive correlation between information processing speed and the downregulation of the four receptor subunits in schizophrenia patients, with correlation coefficients for GABRA1 ($r = 0.871$, $P = 0.023$), GABRB2 ($r = 0.731$, $P = 0.016$), GABRD ($r = 0.641$, $P = 0.032$), and GABRE ($r = 0.543$, $P = 0.018$).

Correlation analysis of GABA receiver subunit downregulation and verbal learning

As shown in Table 4, GABRA1, GABRB2, GABRD, and GABRE were not significantly correlated with word learning ($P > 0.05$) and only GABRA1 was downregulated ($r = 0.734$, $P = 0.023$).

Table 2 Relative changes in gamma aminobutyric acid receptor subunit expression levels in the schizophrenia group

Receptor subunit	FC	P value
GABRA1	-	< 0.001
GABRB2	-	< 0.001
GABRD	-	< 0.001
GABRE	-	< 0.001
GABRA5	0	0.993
GABRA6	0	0.991

FC: Fold change.

Table 3 Correlation analysis of gamma aminobutyric acid receptor subunit downregulation and information processing speed in MATRICS Consensus Cognitive Battery Cognitive Scores

Receptor subunit	Information processing speed	
	r value	P value
GABRA1	1.375	0.023
GABRB2	2.625	0.016
GABRD	1.190	0.032
GABRE	5.364	0.018

Table 4 Correlation analysis gamma aminobutyric acid receptor subunit downregulation and verbal learning in MATRICS Consensus Cognitive Battery Cognitive Scores

Receptor subunit	Verbal learning	
	r value	P value
GABRA1	0.734	0.023
GABRB2	0.075	0.773
GABRD	0.128	0.639
GABRE	0.079	0.833

Correlation analysis of GABA receiver subunit downregulation and working memory

As shown in Table 5, the downregulation of GABRA1 ($r = 0.467$, $P = 0.047$) and GABRB2 ($r = 0.734$, $P = 0.023$) was significantly positively correlated with working memory, while GABRD and GABRE were not correlated ($P > 0.05$).

Correlation analysis of GABA receptor subunit downregulation and attention/vigilance visual learning

As shown in Table 6, only the GABRE ($r = 0.532$, $P = 0.038$) was associated with attention/vigilance in visual learning. GABRA1, GABRB2, and GABRD levels were positively correlated ($P > 0.05$).

Correlation analysis of GABA receptor subunit downregulation and reasoning and problem solving

As shown in Table 7, GABRB2 ($r = 0.992$, $P = 0.098$), GABRD ($r = 1.386$, $P < 0.001$), and GABRE ($r = 0.747$, $P = 0.004$) were positively associated with reasoning and problem solving, whereas GABRA1 and GABRA1 were not correlated ($P > 0.05$).

Correlation analysis of GABA receptor subunit downregulation and social cognition

As shown in Table 8, GABRB2 and GABRE were not significantly correlated with social cognition ($P > 0.05$). However, GABRA1 ($r = 0.871$, $P = 0.006$) and GABRD were significantly downregulated ($r = 0.752$, $P = 0.049$).

Table 5 Correlation analysis of gamma aminobutyric acid receptor subunit downregulation and working memory in MATRICS Consensus Cognitive Battery Cognitive Scores

Receptor subunit	Working memory	
	<i>r</i> value	<i>P</i> value
GABRA1	0.467	0.047
GABRB2	0.623	0.032
GABRD	0.099	0.833
GABRE	0.229	0.681

Table 6 Correlation analysis of gamma aminobutyric acid receptor subunit downregulation and attention/vigilance visual learning in MATRICS Consensus Cognitive Battery Cognitive Scores

Receptor subunit	Attention/vigilance visual learning	
	<i>r</i> value	<i>P</i> value
GABRA1	0.667	0.199
GABRB2	0.210	0.612
GABRD	0.261	0.609
GABRE	0.532	0.038

Table 7 Correlation analysis of gamma aminobutyric acid receptor subunit downregulation and reasoning and problem solving in MATRICS Consensus Cognitive Battery Cognitive Scores

Receptor subunit	Reasoning and problem solving	
	<i>r</i> value	<i>P</i> value
GABRA1	0.651	0.222
GABRB2	0.992	0.098
GABRD	1.386	< 0.001
GABRE	0.747	0.004

Table 8 Correlation analysis of gamma aminobutyric acid receptor subunit downregulation and social cognition in MATRICS Consensus Cognitive Battery Cognitive Scores

Receptor subunit	Social cognition	
	<i>r</i> value	<i>P</i> value
GABRA1	0.871	0.006
GABRB2	0.152	0.707
GABRD	0.752	0.049
GABRE	0.468	0.360

DISCUSSION

In schizophrenia, a person's senses, emotions, and behaviors are chronically and severely affected[21]. Individuals with schizophrenia have impaired ability to distinguish reality from imagination[22]. It may be difficult for them to engage in normal social behaviors because of their slow responses and behavioral withdrawal. Medical professionals classify schizophrenia as a disorder rather than a disease by medical professionals[23,24]. Most cases occur in young or primed individuals. It includes physical, mental, emotional, and behavioral disorders; however, the patient has no evidence of coma or mental retardation[25,26]. The pathogenesis of schizophrenia is complex and various hypotheses have been proposed. Recent studies have gradually shifted classical focus from the dopamine hypothesis to the GABA hypothesis. Signal transmission between most nerve cells in the central nervous system is primarily mediated by glutamate excitation

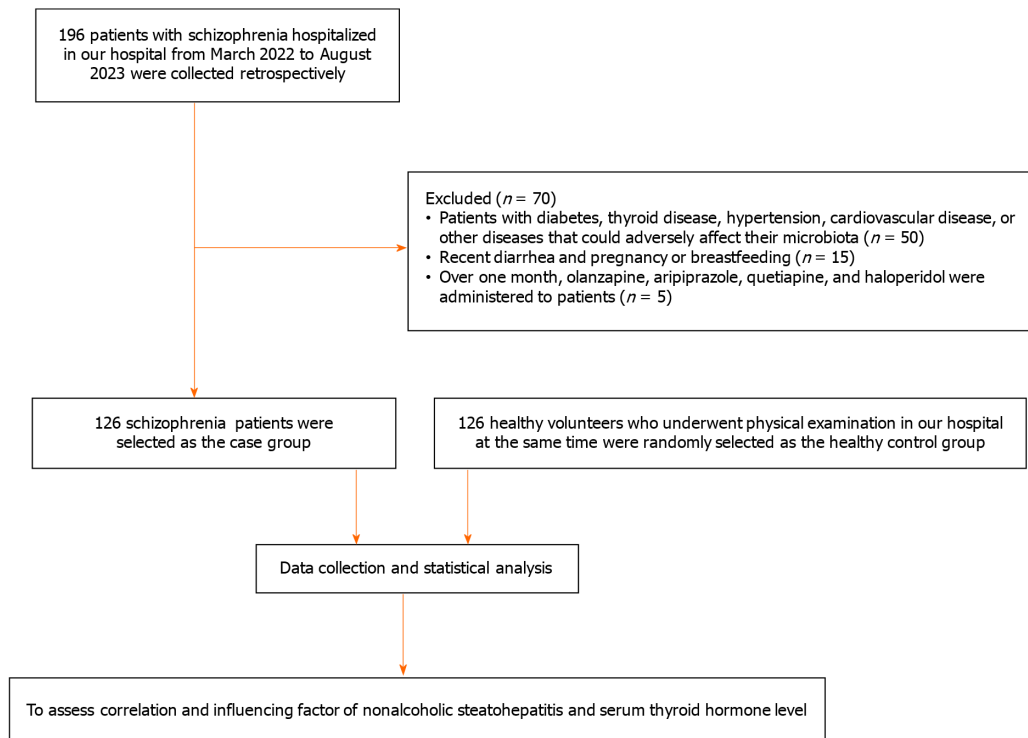


Figure 1 Flow chart of the study.

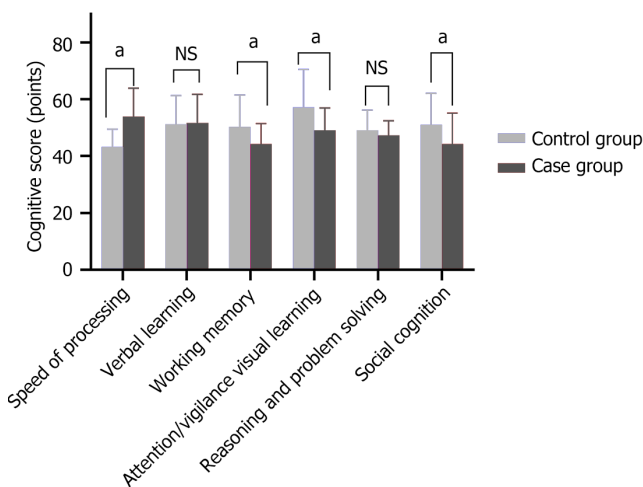


Figure 2 Comparative analysis of cognitive scores between the two groups. ^a $P < 0.05$, ^b $P < 0.01$, NS: Not significant.

and GABA inhibition mode[27]. GABA is produced from glutamate under the action of glutamate decarboxylase, and is abundantly expressed in the central nervous system[28]. Cl^- are pumped out through the $\text{Na}^+/\text{K}^+/\text{Cl}^-$ pump transporter, which reduces the intracellular Cl^- concentration and causes the hyperpolarization of neurons. Failure to maintain the glutamate-GABA balance may be related to schizophrenia, epilepsy, and anxiety[29]. Glutamate-GABA regulates the neuronal excitation-inhibition balance, which can cause neurodegenerative diseases and cognitive impairment[30]. Reversing GABA imbalance, inhibiting the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells signaling pathway, and inhibiting the release of interleukin-6 and tumor necrosis factor- α can improve cognitive impairment[31].

Patients with schizophrenia often experience cognitive impairments, such as difficulty integrating information, memory loss, and difficulty paying attention. Most individuals with cognitive dysfunction further experience memory decline as a primary symptom[32]. In addition, schizophrenia impairs executive function, visuospatial ability, comprehension, and numeracy. Age affects both general and social cognition[33]. The incidence of cognitive dysfunction increases with the aging population grows[34]. Several clinical studies have demonstrated a correlation between schizophrenia and cognitive function. Interventions targeting cognition, emotions, and social aspects have shown promising results[35]. This study observed a substantial decline in various cognitive aspects of patients with schizophrenia.

Compared to healthy individuals, we observed impairments in learning, memory, fine motor skills, social cognition, working memory, category fluency, information processing, and kinetic energy. These results suggest an association between cognitive function and schizophrenia, similar to the results of the above study.

In addition, this study found that the downregulation of the GABA receptor subunit strongly affects schizophrenia symptoms and the risk of development. This finding supports the important role of the GABA system in the pathogenesis of schizophrenia, which is consistent with previous studies[36]. GABA is one of the most important inhibitory neurotransmitters in the central nervous system and plays a neuroregulatory role by binding to its receptors[37]. Changes in the expression of GABA receptor subunits may affect the inhibitory effect on neurons, leading to a variety of symptoms in patients with schizophrenia. According to these results, the downregulation of GABRA1, GABRB2, GABRD, GABRE, and other subunits may affect GABA receptor function, thereby affecting neuronal inhibitory effects[38]. Such changes may promote neuronal instability, leading to abnormalities in thinking, emotions, and behavior in people with schizophrenia. In addition, the expression levels of GABA receptor subunits may also be influenced by environmental factors, such as drugs, diet, and stress, which may also be involved in the pathogenesis of schizophrenia.

Limitations

This study has several limitations. Firstly, we only explored the correlation between GABA receptor subunits and schizophrenia in terms of gene expression, and the small sample size led to genetic analysis being the only method used to determine the results. Therefore, our study is only in the initial stages of exploring the relationships between genetic alterations. More comprehensive studies on these genes are needed to determine their exact roles in schizophrenia. Furthermore, other possible factors (such as environmental factors and nerve cell apoptosis, *etc.*) were not investigated. The pathogenesis of schizophrenia can be understood better by examining the effects of various factors. Further research is required to determine the interactions between different GABA receptor subunits and their effects on schizophrenia.

CONCLUSION

In conclusion, this study found that the downregulation of GABA receptor subunits is closely related to the risk and symptom severity of schizophrenia, providing a new perspective to further understand the pathogenesis of schizophrenia. Future studies are needed to further investigate the abnormal expression levels and function of GABA receptor subunits and the relationship between GABA receptor subunits and environmental factors, nerve cell apoptosis, and other factors to reveal the pathogenesis of schizophrenia more comprehensively. At the same time, the development of therapeutic strategies targeting GABA receptor subunits also needs further research and practice. Overall, the results of this study suggests that the downregulation of GABA receptor subunits is closely associated with the risk of onset and symptom severity in schizophrenia. These findings contribute to a deeper understanding of schizophrenia pathogenesis and provide a theoretical basis for developing new treatment strategies. Researchers must account for the effects of various factors on schizophrenia to better understand its pathogenesis.

FOOTNOTES

Author contributions: Chen X performed the majority of experiments and wrote the manuscript; Zhou YN and Lu XZ designed the study and corrected the manuscript; Li RJ is involved in analytical tools; Xiong YF and Sheng X participated to the collection of the human material; Zhu WW served as scientific advisor and participate to the collection of human material.

Institutional review board statement: The study was approved by the ethics committee of Brain Hospital of Hunan Province (Approval No. 2023338).

Informed consent statement: All patients gave informed consent.

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

Data sharing statement: Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at q1640809558@163.com.

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

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Chen YX

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Case Control Study

Association of serum interleukin-6 with negative symptoms in stable early-onset schizophrenia

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Morozova MA, Russia

Received: March 12, 2024

Revised: April 28, 2024

Accepted: May 17, 2024

Published online: June 19, 2024

Processing time: 99 Days and 0.3 Hours



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Abstract

BACKGROUND

Accumulating evidence suggests that the inflammatory cytokine interleukin-6 (IL-6) contributes to the pathophysiology of psychiatric disorders. However, there was no study concerning the relationship between IL-6 concentrations and clinical features in the chronic phase of early-onset schizophrenia (EOS).

AIM

To investigate the relationship between serum IL-6 concentration and the clinical

features of EOS.

METHODS

We measured serum IL-6 Levels from 74 patients with chronic schizophrenia, including 33 with age at onset < 21 years (EOS group) and 41 with onset ≥ 21 years in [adult-onset schizophrenia (AOS) group], and from 41 healthy controls. Symptom severities were evaluated using the Positive and Negative Syndrome Scale (PANSS).

RESULTS

Serum IL-6 concentrations were higher in both EOS and AOS groups than healthy controls ($F = 22.32$, $P < 0.01$), but did not differ significantly between EOS and AOS groups ($P > 0.05$) after controlling for age, body mass index, and other covariates. Negative symptom scores were higher in the EOS group than the AOS group ($F = 6.199$, $P = 0.015$). Serum IL-6 concentrations in the EOS group were negatively correlated with both total PANSS-negative symptom score ($r = -0.389$, $P = 0.032$) and avolition/asociality subscore ($r = -0.387$, $P = 0.026$).

CONCLUSION

Patients with EOS may have more severe negative symptoms than those with adult-onset schizophrenia during the chronic phase of the illness. IL-6 signaling may regulate negative symptoms and its avolition/asociality subsymptoms among the early-onset chronic schizophrenic patients.

Key Words: Early-onset schizophrenia; Interleukin 6; Negative symptoms; Avolition; Asociality

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Core Tip: In this study, we focus on the negative symptoms and inflammatory levels in the chronic stage of early-onset schizophrenia. Patients' clinical symptoms were assessed by the Positive and Negative Syndrome Scale, and the level of inflammation was assessed by serum interleukin-6 (IL-6) Levels. Our study found that patients with early-onset schizophrenia may have more severe negative symptoms than those with adult-onset schizophrenia during the chronic phase of the illness. IL-6 signaling may regulate negative symptoms and its avolition/asociality subsymptoms among the early-onset chronic schizophrenic patients.

Citation: Chen P, Yang HD, Wang JJ, Zhu ZH, Zhao HM, Yin XY, Cai Y, Zhu HL, Fu JL, Zhang XZ, Sun WX, Hui L, Zhang XB. Association of serum interleukin-6 with negative symptoms in stable early-onset schizophrenia. *World J Psychiatry* 2024; 14(6): 794-803

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/794.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.794>

INTRODUCTION

Schizophrenia is a neuropsychiatric disorder of complex etiology with lifetime incidence of about 0.4% and total global prevalence of approximately 1%[1]. Symptoms of the disease are stratified into three domains, positive, negative, and cognitive, with substantial variation in severity among individual patients. Furthermore, these distinct symptom domains can have unique effects on clinical course and outcome. For instance, negative symptoms such as flat affect and asociality impair social functioning[2]. Several schizophrenia subtypes have been defined based on predominant symptom profiles and clinical course, including early-onset schizophrenia (EOS) with age of onset before 21 years[3,4]. According to an der Heiden and Häfner[5], about 41% of patients develop their first symptoms before the age of 20, and numerous studies have found that EOS was associated with more severe negative symptoms, more frequent relapses, poorer social functioning, and worse overall prognosis[6-8]. While the pathological mechanisms contributing to poor outcome among EOS patients are still largely unknown, Fraguas *et al*[9] reported more severe inflammation and oxidative stress in this patient group.

Exploratory factor analyses of Positive and Negative Syndrome Scale (PANSS) scores have revealed two negative subsymptom clusters[10-13], expression deficits and avoidance/asociality, with possibly distinct underlying pathological mechanisms. Therefore, uniform treatment strategies for all EOS patients regardless of individual negative symptom profile may produce suboptimal clinical outcomes[11]. The expression cluster includes flat affect, poor rapport, lack of spontaneity, mannerisms and posturing, motor retardation, and avolition, while the asociality factor consists of emotional withdrawal, passive/apathetic social withdrawal, and active social avoidance. The first factor reflects a loss of initiative, and the second factor social amotivation related to community interaction[14]. Based on these findings, we speculated that indices of neuroinflammation will be larger in chronic EOS patients compared to adult-onset schizophrenia (AOS) patients and associated with negative symptom severity. The current study focused primarily on expression deficits and avolition/asociality symptoms.

The inflammatory hypothesis of schizophrenia posits that low grade inflammation contributes to disease course and symptom expression[15-18], and is supported by studies showing higher levels of pro-inflammatory factors such as cytokines in the blood and cerebrospinal fluid of schizophrenia patients. A large epidemiological study also found that severe infections and autoimmune disorders were risk factors for schizophrenia[15,19], while the largest genome-wide association study to date identified 108 Low effect-size risk loci, most of which were associated with inflammatory responses[20].

Interleukin-6 (IL-6) is a highly pleiotropic cytokine involved in multiple aspects of the inflammatory response, including neurotoxicity and neuroprotection[21-23], depending on context. For example, IL-6 overexpression inhibited hippocampal neurogenesis[24], while blockade of IL-6 but not tumor necrosis factor- α (TNF- α) enhanced adult hippocampal neurogenesis by up to 50%[25]. Such findings suggest that IL-6 release from activated microglia is a core regulator of neurogenesis throughout life. Similarly, IL-6 release from microglia is known to maintain chronic inflammation in models of autoimmune encephalitis and various neurological diseases[26]. Recent Mendelian studies have also found that genetically predicted IL-6 signaling strength is likely to influence brain structural changes associated with increased schizophrenia risk[27,28]. Gallego *et al*[29] reported that these changes in serum IL-6 were consistent with cerebrospinal fluid IL-6, suggesting that less invasive blood samples can be used routinely to assess IL-6 activity as a marker for prognosis. A positive correlation was also found between serum IL-6 Levels and negative symptom severity in drug-naïve male schizophrenics[30], while a study of Chinese patients with chronic schizophrenia found that IL-6 concentration was positively correlated with negative symptom scores at both admission and discharge[31]. Golimbet *et al*[32] further reported a correlation between the IL-6 -174 G/C polymorphism and greater avolition and apathy scores among schizophrenia patients. Based on these findings, we speculated that IL-6 Likely contributes to the unique clinical symptoms of chronic phase EOS, but to our best knowledge the associations of serum IL-6 with negative symptom have not been examined in Asian EOS patients.

MATERIALS AND METHODS

Subjects and assessments

Schizophrenia inpatients were recruited from Guangji Hospital, Suzhou, China, from January 2016 to October 2019. Inclusion criteria were as follows: (1) Age 18–75 years; (2) Meeting the Diagnostic and Statistical Manual of Mental Disorders-IV diagnostic criteria for schizophrenia as determined by two psychiatrists using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID); (3) Disease duration of at least 5 years; (4) Han Chinese ethnicity; (5) Taking stable doses of antipsychotic drugs for at least one year (primarily clozapine, phenazine, risperidone, sulpiride, haloperidol, and chlorpromazine (CPZ)); and (6) Agreeing to voluntarily participation with informed written consent. Exclusion criteria were: (1) Comorbid somatic disorders or substance dependence; and (2) Not completing primary education. A demographic assessment questionnaire was used to gather enrollment data, including sex, age, years of education, smoking status/history, body mass index (BMI), age of onset, and duration of illness.

Forty-one healthy controls (HCs) were recruited during the same period from Suzhou local communities through media and pamphlet advertisements. A psychiatrist confirmed health status and family psychiatric history using an unstructured clinical interview. Candidates with relevant physical and mental health problems were excluded. Enrolled candidates provided written informed consent for participation. The study protocol and informed consent form were approved by the Institutional Review Board of a Suzhou City-owned Mental Hospital (No. 2022005).

Definitions of groups

Participants with schizophrenia were asked to identify the age at first acute psychotic symptoms during the SCID, and this information was confirmed by medical records. We divided these patients into an EOS group if age at first psychotic episode occurred before age 21 and an AOS group if first psychotic episode occurred at 21 years or older[3,4,33]. The EOS group included 33 patients (23 males and 10 females) and the AOS group included 41 patients (24 males and 24 females).

Definitions of two subdomains of negative symptom

Exploratory factor analysis yielded a two-factor structure of negative symptoms. The first factor, expressive deficits, consisted of PANSS items N1, N3, N6, G5, G7, and G13, while the second factor, avolition/asociality, consisted of PANSS items N2, N4, and G16[10,34].

Clinical assessment

To ensure the reliability and consistency of assessments across the study period, two psychiatrists with at least 5 years of clinical experience attended a training course on the use of the PANSS. After training, the interobserver correlation coefficient for the PANSS score was maintained above 0.8.

Measurement of serum IL-6 level

Peripheral venous blood samples were drawn from patients and HCs between 7 and 9 AM after an overnight fast, and centrifuged at 3000 rpm for 15 min in procoagulant and anticoagulant tubes to isolate serum and plasma fractions, respectively. The samples were then stored at -80 °C until analysis. Serum IL-6 concentrations were measured using a BDTM FACSCanto Flow Cytometer and BDTM Cytometric Bead Array (CBA) Human Inflammatory Cytokines Kit (BD

Biosciences, San Jose, CA, United States) according to the manufacturers' instructions. A standard curve was also constructed for each sample batch from triplicate measurements of known IL-6 concentrations using the supplied BDTM CBA Human Inflammatory Cytokine Standards. All measurements were performed by the same technician who was blinded to donor identity and clinical information.

Statistical analyses

Statistical analyses were conducted using Statistical Product and Service Solutions 25.00. All datasets were first examined for normality using the Kolmogorov-Smirnov test. Based on results indicating non-normally distributed serum IL-6 concentrations for both EOS and AOS patients and HCs (all $P < 0.05$ by Kolmogorov-Smirnov test), values were converted to natural logarithm values for analysis. Serum log IL-6 concentrations were compared among EOS patients, AOS patients, and HCs by multivariate analysis of covariance (MANCOVA) with diagnosis as a fixed factor, and age, sex, and BMI as covariates. Other continuous variables were compared by Student's *t*-test or one-way analysis of variance, while categorical variables were compared by chi-square test. Results were corrected for multiple comparisons using the Bonferroni method. Associations between variables were evaluated by calculating Pearson's correlation coefficients. Exploratory multiple regression analysis was also performed to examine the relationship between serum log IL-6 and PANSS scores after controlling for age, gender, and BMI as covariates. A corrected $P < 0.05$ (two-tailed) was considered statistically significant for all tests.

RESULTS

Demographic data and clinical characteristics

Chronic schizophrenia inpatients were divided into an early-onset group (EOS group, $n = 33$) with first psychotic episode before 21 years of age and an adult-onset group (AOS group, $n = 41$) with first psychotic episode after 21 years of age. A HC group (HC group, $n = 41$) was also recruited as a control. The demographic and clinical characteristics of all three study groups are summarized in [Table 1](#). There was no significant difference in sex ratio and number of smokers among groups ($P > 0.05$). As expected, there were significant group differences in age, years of education, and BMI ($P < 0.05$), but neither years of education, duration of disease, nor CPZ equivalent dose differed between EOS and AOS groups ($P > 0.05$). According to the criterion for group stratification, age at schizophrenia onset was significantly older in the AOS group. Mean BMI was higher in the EOS group than the AOS group ($P < 0.05$), and so was included as a fixed effect covariate in subsequent analyses.

As shown in [Figure 1A](#), serum log IL-6 concentrations were higher in both EOS and AOS groups compared to the HC group ($P < 0.001$) but did not differ between EOS and AOS groups ($P > 0.05$).

Associations of serum log IL-6 concentrations with clinical symptoms in EOS and AOS patients

In the EOS group, serum log IL-6 concentration was negatively correlated with total PANSS-negative symptom score ($r = -0.389$, $P = 0.032$; [Figure 1B](#)) and with avolition/asociality subscore ($r = -0.387$, $P = 0.026$; [Figure 1C](#)). Furthermore, the correlation between total PANSS-negative score and serum log IL-6 concentration remained significant after controlling for age, years of education, BMI, smoking status, age of onset, duration of illness, and CPZ equivalence dose ($R^2 = 0.151$, $P = 0.025$). This association was also significant in stepwise multiple regression analysis ($R^2 = 0.150$, $P = 0.026$). In contrast, no such association was found between clinical factors and serum log IL-6 concentration in the AOS group.

DISCUSSION

The main findings of the present study were as follows: (1) Serum IL-6 concentrations were elevated in both EOS and AOS patient groups compared to a control group but did not differ between patient groups; (2) total PANSS-negative score (sum of subscores) was significantly higher in the EOS group than the AOS group, indicating more severe negative symptoms; and (3) total PANSS-negative symptom score and Avolition/Asociality subscore were correlated with serum log IL-6 concentration in the EOS group but not the AOS group. These results suggested that IL-6 inflammatory signaling regulated negative symptom severity in EOS patients. To our knowledge, this is the first study to find an association between serum IL-6 concentration and PANSS-negative symptom severity in EOS patients during chronic stabilization.

BMI in patients with EOS and AOS

Many patients receiving antipsychotic treatments experience unhealthy weight gain, and we found a significant BMI elevation among EOS patients during the first unmedicated phase compared to AOS patients. Lang *et al* [35] found no significant difference in BMI between EOS patients during the first unmedicated phase and AOS patients, but did identify BMI as a risk factor for metabolic syndrome in EOS. A prospective study by Ratzoni *et al* [36] also found that olanzapine and risperidone induced greater weight gain in Israeli adolescent patients than adult patients. Thus, weight gain should be closely monitored in EOS patients. We speculate that elevated BMI in the chronic phase of EOS may contribute to poorer outcome. Obesity is also associated with elevated serum IL-6, although the correlation between IL-6 and total PANSS-negative symptoms among EOS patients remained significant after controlling for BMI as well as other covariates. Nonetheless, further studies are needed to comprehensively assess the influences of confounding factors on BMI in schizophrenia, such as different types of medications, age, ethnicity, duration of illness, and sex.

Table 1 Demographic and clinical characteristics of early-onset schizophrenia patients, adult-onset schizophrenia patients, and healthy controls

	Early-onset schizophrenia	Adult-onset schizophrenia	Healthy control	Statistic (F/χ^2)	P value
Sex					
Male	23	24	23	1.57	0.46 ¹
Female	10	17	18		
Smoking					
Smoker	7	13	15	2.09	0.35 ¹
Nonsmoker	26	28	26		
Age (yr) ^a	38.79 ± 9.21	46.14 ± 7.26	42.61 ± 10.30	5.00	0.008 ²
Educations (yr) ^b	9.64 ± 2.50	9.10 ± 2.96	12.24 ± 2.61	20.78	< 0.001 ²
BMI (kg/m ²) ^b	28.57 ± 4.87	25.56 ± 3.74	23.26 ± 2.72	17.88	< 0.001 ²
Age of onset (yr) ^b	17.00 ± 2.75	28.22 ± 5.69		107.67	< 0.001 ²
Duration of illness (yr)	21.61 ± 9.22	17.88 ± 7.29		3.78	0.056 ²
Dose of CPZ equivalent (mg/d)	653.37 ± 300.04	704.85 ± 311.41		0.52	0.475 ²
PANSS					
Positive subscores	14.54 ± 5.95	14.73 ± 6.71		1.60	0.21 ³
Negative subscores ^a	20.85 ± 5.56	18.15 ± 3.86		6.20	0.015 ³
General subscores	33.21 ± 9.32	31.05 ± 8.24		0.16	0.688 ³
Total scores	68.61 ± 17.90	63.93 ± 14.23		0.004	0.953 ³
Expressive deficits	16.33 ± 4.77	14.17 ± 3.26		3.26	0.075 ³
Avolition/asociality	9.52 ± 3.72	8.44 ± 2.44		2.05	0.157 ³
Log IL-6 level ^b	0.88 ± 0.37	0.81 ± 0.40	0.18 ± 0.03	22.32	< 0.001 ³

^a $P < 0.05$.^b $P < 0.001$.¹ χ^2 test.²One-way analysis of variance.³The P values for Positive and Negative Symptom and log interleukin-6 were adjusted for age, sex, and body mass index.

Mean ± SD are reported for all variables. BMI: Body mass index; CPZ: Chlorpromazine; PANSS: Positive and Negative Symptom; IL-6: Interleukin-6.

Negative symptom in patients with EOS and AOS

Negative symptom scores were higher in the EOS group than the AOS group, consistent with several previous relevant studies [8,37–40] but at odds with several others reporting no difference [41–43]. These disparities may be related to sample heterogeneity (*e.g.*, ethnic background, first-episode or relapse, anti-psychotic drug dose, hospitalized *vs* outpatient, and illness severity). Nonetheless, the current research suggests that intervention for the chronic phase of EOS should place greater emphasis on negative symptoms.

Serum IL-6 Levels in patients with EOS and AOS

Serum IL-6 concentrations were higher in both EOS and AOS patient groups compared to healthy matched controls, suggesting that schizophrenia was associated with a chronic inflammatory response independent of onset age and consistent with the inflammation hypothesis of schizophrenia. Of the few previous studies on serum IL-6 in EOS patients, one found no difference between first-episode EOS and healthy individuals [44], while a clinical two-sample Mendelian randomized study found increased soluble IL-6 receptor levels in patients, which can be explained as a compensatory response to IL-6 elevation [45]. Elevated serum IL-6 suggests microglial cell hyperactivity [26] in the chronic phases of EOS and AOS. While additional studies with larger samples are needed for verification, it appears that elevated serum IL-6 concentration is a ubiquitous feature of stable chronic schizophrenia.

Associations of serum log IL-6 concentrations with clinical symptoms in EOS and AOS patients

Numerous studies have found strong associations between elevated IL-6 and both the development and progression of first-episode psychosis in acute and chronic stages of schizophrenia, suggesting that inflammatory cascade responses contribute to the underlying pathogenesis and symptom expression [18,46]. Indeed, some investigations have found correlations with positive symptoms, negative symptoms, depressive symptoms, and cognitive deficits [47]. A meta-

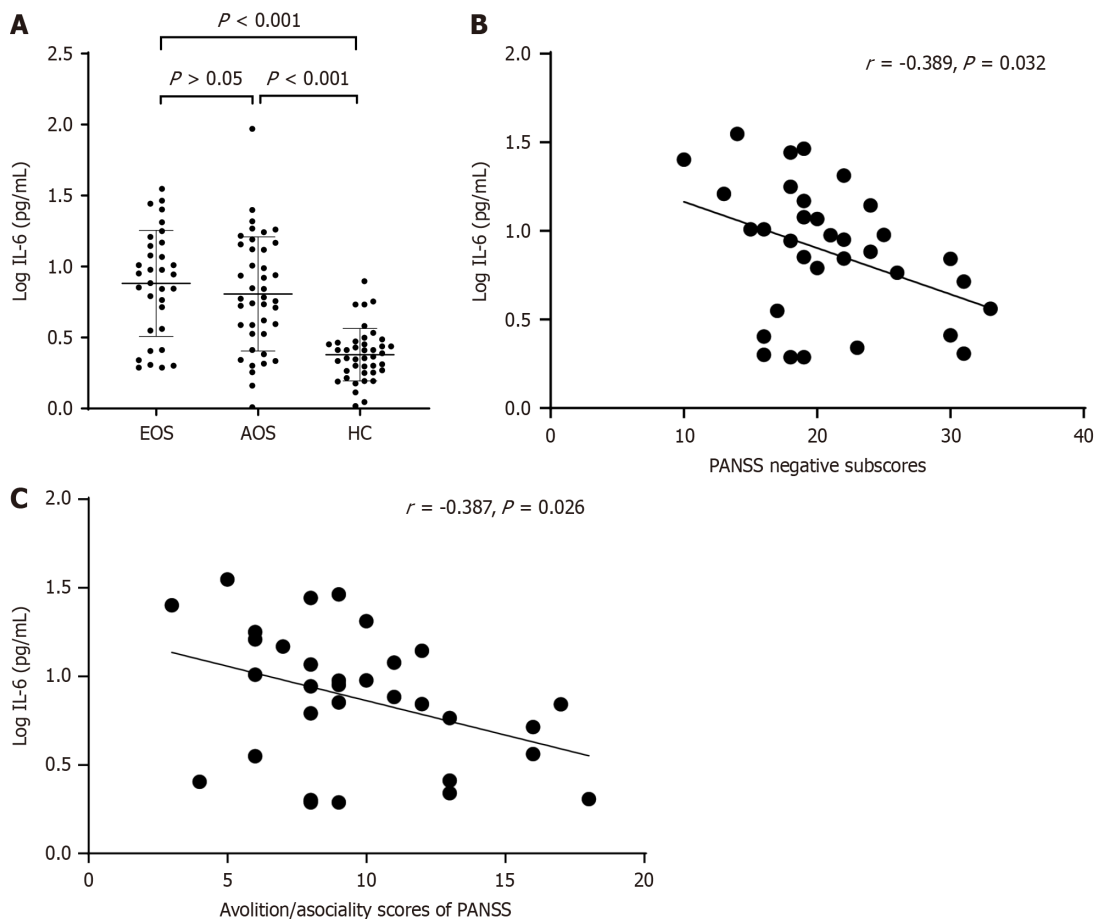


Figure 1 Comparison of serum Log interleukin-6 Levels and the relationship with clinical symptoms in different subject groups. A: Serum log interleukin-6 (IL-6) concentrations in chronic early-onset schizophrenia (EOS) patients, chronic adult-onset schizophrenia patients, and healthy controls (HCs). Concentrations were significantly higher in schizophrenia groups than HCs but did not differ between schizophrenia groups; B: Correlation between serum log IL-6 concentration and total Positive and Negative Syndrome Scale (PANSS)-negative scores in the EOS patient group; C: Correlation between serum log IL-6 concentration and PANSS Avolition/Asociality subscore in the EOS patient group. IL-6: Interleukin-6; EOS: Early-onset schizophrenia; HC: Healthy control; PANSS: Positive and Negative Syndrome Scale; AOS: Adult-onset schizophrenia.

analysis concluded that the IL-6 elevation in patients with first-episode psychosis or acute relapse normalized after antipsychotic treatment[48]. Thus, variations in IL-6 Levels may reflect complex immunoregulatory functions at different stages of the disease. However, we found that higher serum IL-6 concentrations in stably medicated EOS patients were associated with both lower overall PANSS-negative symptom severity and avolition/asociality severity, while most previous investigations have found either a positive correlation or no relationship[48-50]. Stojanovic *et al*[51] did report a negative correlation with PANSS positive subscale scores (but positive correlations with PANSS-negative subscale scores) among outpatients with psychotic disorders, while Gibson *et al*[52] found a negative correlation between serum IL-6 and PANSS total score as well as positive and negative subscales in patients with cannabinoid-positive acute psychiatric disorders. As mentioned, Golimbet *et al*[32] found a link between the IL-6 -174 G/C polymorphism and both dementia and apathy scores that approached significance. To our best knowledge, the current case-control study is the first to find negative correlations between serum IL-6 and both total PANSS-negative symptom score and avolition/asociality subscore among patients with chronic stage EOS.

These discrepancies across studies may reflect the pleiotropic activity of IL-6 signaling in immune regulation[21-23,53, 54]. IL-6 can modulate cellular responses in two ways. In the classical signaling pathway, IL-6 binds to its cognate cell membrane receptor (IL-6R) and triggers a heterodimeric association with two membrane-bound gp130 molecules, which in turn initiates downstream pro- and anti-inflammatory responses through activation of three signaling cascades, most prominently the JAK-STAT pathway. Alternatively, in the trans-signaling pathway, IL-6 binds to the soluble form of its receptor (sIL-6R) before forming a complex with membrane-bound gp130. This complex then activates downstream pathways leading to pro-inflammatory responses. However, soluble gp130 (sgp130) inhibits trans-signaling by blocking the association of the IL-6/sIL-6R complex with membrane-bound gp130 molecules[54]. Szabo *et al*[53] reported significantly higher soluble sgp130 concentrations in schizophrenic patients who used cannabis. We propose that IL-6 trans-signaling may regulate negative symptoms and sub-symptoms in the chronic phase of EOS. Negative symptoms are a multidimensional construct with potentially complex interactions between subtypes and with other symptom domains. Serum IL-6 concentrations may also be influenced by genetic differences and psychotropic substance use among other factors not examined in the current study. In addition, differences in study design and methodology may explain these discrepancies with previous studies, including the participant selection process, the time point and method of IL-6

measurement, and the selection of covariates for statistical analyses. This unexpected finding challenges our traditional view of IL-6 signaling function in EOS and suggests that future work must examine the functions of this cytokine in different disorder subtypes, phases, and treatment conditions to identify the context-specific effects on clinical course and symptom expression.

CONCLUSION

We examined serum IL-6 concentrations in patients with EOS and AOS in the chronic phase. Our study demonstrated that serum IL-6 concentrations were elevated in both EOS and AOS patient groups compared to a control group but did not differ between patient groups. Moreover, total PANSS-negative score was significantly higher in the EOS group than the AOS group, indicating more severe negative symptoms. In addition, we found that the mean BMI was higher in the EOS group than the AOS group. And total PANSS-negative symptom score and Avolition/Asociality subscore were correlated with serum log IL-6 concentration in the EOS group but not the AOS group. These results suggested that IL-6 inflammatory signaling regulated negative symptom severity in EOS patients. The present study had several limitations. First, the sample size was relatively small, limiting statistical power. Therefore, more subtle associations and differences may have been missed. Second, although we did not find a relationship between drug treatment (in clozapine equivalents) and IL-6 concentration, such associations may have been influenced by uncontrolled clinical factors, such as drug type, dose, and treatment duration. Third, our findings were essentially cross-sectional, and future longitudinal studies should be conducted to establish causal relationships. Finally, we evaluated only IL-6, while it is known that cytokine signaling factors interact to determine the ultimate inflammatory status. Despite these limitations, the present study suggested that negative symptoms were more severe in EOS compared to AOS and that IL-6 was involved in the underlying pathomechanism.

ACKNOWLEDGEMENTS

We would like to thank all participants and all co-authors in this study.

FOOTNOTES

Author contributions: Chen P, Yang HD and Wang JJ were responsible for data collection, data curation, and writing original draft; Chen P, Yang HD, Wang JJ, Sun WX and Zhao HM performed the statistical analysis; Zhu ZH, Cai Y and Yin XY were responsible for performing the clinical rating; Zhu HL, Fu JL and Zhang XZ were responsible for recruiting the patients, and collecting the samples; All authors reviewed the manuscript. Hui L and Zhang XB were co-corresponding authors; Zhang XB was responsible for study design, statistical analyses, and editorial revisions; Hui L was responsible for study design, patient recruitment, funding acquisition, supervision, and editing.

Supported by National Natural Science Foundation of China, No. 82371508 and No. 81771439; Jiangsu Provincial Key Research and Development Program, No. BE2020661; Suzhou Municipal Health Commission Science Research Program, No. GSW2020095; National Mentorship Training Programme for Young Health Professionals, No. Qngg2022027; Suzhou Clinical Key disciplines for Geriatric Psychiatry, No. SZXK202116; Suzhou Clinical Medical Center for Mood Disorders, No. Szlcycxz202109; Suzhou Key Technologies Program, No. SKY2021063; Suzhou Municipal Science and Technology Bureau Program, No. SKJY2021142, No. SKJY2021143, No. SKY2023227, No. SKY2022064 and No. SKYD2023159; Suzhou Key Disease Diagnosis and Treatment Program, No. LCZX202218.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Suzhou Guangji Hospital Institutional Review Board, Approval No. 2022005.

Informed consent statement: All clinical trials were obtained informed consent.

Conflict-of-interest statement: No conflict of interest was disclosed for each author.

Data sharing statement: The data are available from the corresponding author on reasonable request.

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

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S-Editor: Li L

L-Editor: A

P-Editor: Zheng XM

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Case Control Study

Identification of male schizophrenia patients using brain morphology based on machine learning algorithms

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Singh A

Received: March 15, 2024

Revised: May 1, 2024

Accepted: May 21, 2024

Published online: June 19, 2024

Processing time: 96 Days and 10 Hours



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Abstract

BACKGROUND

Schizophrenia is a severe psychiatric disease, and its prevalence is higher. However, diagnosis of early-stage schizophrenia is still considered a challenging task.

AIM

To employ brain morphological features and machine learning method to differentiate male individuals with schizophrenia from healthy controls.

METHODS

The least absolute shrinkage and selection operator and *t* tests were applied to select important features from structural magnetic resonance images as input features for classification. Four commonly used machine learning algorithms, the general linear model, random forest (RF), k-nearest neighbors, and support vector machine algorithms, were used to develop the classification models. The performance of the classification models was evaluated according to the area under the receiver operating characteristic curve (AUC).

RESULTS

A total of 8 important features with significant differences between groups were considered as input features for the establishment of classification models based on the four machine learning algorithms. Compared to other machine learning algorithms, RF yielded better performance in the discrimination of male schizophrenic individuals from healthy controls, with an AUC of 0.886.

CONCLUSION

Our research suggests that brain morphological features can be used to improve the early diagnosis of schizophrenia in male patients.

Key Words: Schizophrenia; Machine learning; Classification; Structure; Magnetic Resonance imaging

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Core Tip: Schizophrenia is a severe psychiatric disease characterized by impairments in cognition, positive and negative symptoms, affecting about 1% of the general population worldwide. A fast diagnosis of schizophrenia is crucial to prescription of an appropriate anti-psychotic in the early stage, which is able to make treatment more efficient. Many studies have demonstrated widespread functional and structural brain alternations from magnetic resonance imaging in individuals with schizophrenia in relation to healthy controls. our aims were to employ four commonly used machine learning algorithms including general linear model, random forest, k-nearest neighbors, and support vector machine and a wider range of brain morphological features to avoid bias towards a particular machine learning algorithm and improve the performance of classification between male individuals with schizophrenia and healthy controls in the present study.

Citation: Yu T, Pei WZ, Xu CY, Deng CC, Zhang XL. Identification of male schizophrenia patients using brain morphology based on machine learning algorithms. *World J Psychiatry* 2024; 14(6): 804-811

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/804.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.804>

INTRODUCTION

Schizophrenia is a severe psychiatric disease characterized by impairments in cognition and positive and negative symptoms, and it affects approximately 1% of the general population worldwide[1,2]. A fast diagnosis of schizophrenia is crucial for the early-stage prescription of an appropriate antipsychotic agent, which can improve treatment efficacy[3]. Currently, the diagnosis of schizophrenia is carried out based on doctors' judgment through observing the behaviors and psychiatric symptoms of patients[4-7]. However, in many cases, the diagnosis is not highly reliable due to clinician subjectivity, patient heterogeneity and nomenclature inadequacy, and the diagnosis of schizophrenia in the early stages is still considered a challenging task.

Many studies have found widespread functional and structural brain alterations from magnetic resonance imaging (MRI) data in individuals with schizophrenia in comparison to healthy controls[8-12]. Among various MRI techniques, structural MRI, which has the advantages of high spatial resolution, low cost and low sensitivity to noise, has been widely applied to detect differences in brain structures between schizophrenia patients and normal controls. For example, a multimodal meta-analysis with a sample of 801 schizophrenia patients and 957 healthy controls showed that patients with schizophrenia exhibited gray matter volume (GMV) abnormalities in many brain regions relative to healthy controls [13]. One multicenter meta-analytic study including 572 first-episode psychosis (FEP) patients and 502 healthy controls collected from 5 sites showed decreased GMV in the fronto-temporal, insular and occipital regions bilaterally in FEP patients compared to healthy controls[14]. Takayanagi *et al*[15] reported decreased cortical thickness in the frontal and temporal regions in schizophrenia patients compared to healthy controls. Although these abnormal brain structures were detected based on group-level statistical analyses, it is difficult to identify persons at high risk for schizophrenia at the individual level.

Machine learning, as a computational technique, can learn from data inputs and deliver a solution automatically. It is able to overcome the drawbacks of conventional statistical analysis and calculate the probability of an individual being diagnosed with a disease[16-18]. To date, a few studies using machine learning-assisted MRI characterization have attempted to provide diagnostic information for individual patients[19-24]. However, the majority of these studies utilized only a single machine learning algorithm to perform the classification and did not confirm whether the selected machine learning algorithm was optimal. This is because machine learning uses a series of algorithms, and each algorithm has unique methodologies for data processing and model development[25]. In addition, the number of MRI features extracted for discriminating schizophrenic individuals from healthy controls varies between studies. Considering that the type of data is closely associated with the performance of each algorithm[26], our aims in the present study were to employ four commonly used machine learning algorithms, namely, the general linear model (GLM), the random forest (RF), k-nearest neighbors (KNN), and the support vector machine (SVM), with a wide range of brain morphological features to avoid bias toward a particular machine learning algorithm and improve the classification performance in discriminating male individuals with schizophrenia from healthy controls.

MATERIALS AND METHODS

Participants

A total of 78 male subjects, 60 patients with schizophrenia and 18 healthy controls, participated in this study. The patients diagnosed with schizophrenia were recruited from inpatient units of Hefei Fourth People's Hospital from July 2021 to December 2021. The inclusion criteria were as follows: Meeting the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders-5 and right-handedness. In addition, healthy controls were recruited from the community *via* advertisements. The inclusion criteria were as follows: Willingness to participate in the study, no history of any psychiatric disorder, and no family history of psychosis in first-degree relatives. The exclusion criteria for patients with schizophrenia and healthy controls were as follows: Intellectual disability, severe contraindications for MRI, left-handedness, substance abuse, and a history of head injuries. This study was approved by the ethics committee of Hefei Fourth People's Hospital, and all participants provided written informed consent.

MRI acquisition

The structural MRI data of all subjects were collected on a 3.0-Tesla Siemens MRI scanner at Hefei Fourth People's Hospital. T1-weighted images were collected with the following sequence: repetition time = 8.5 ms, echo time = 3.2 ms, inversion time (TI) = 450 ms, flip angle (FA) = 12°, field of view = 256 mm × 256 mm, matrix size = 256 × 256, slice thickness = 1 mm, no gap, voxel size = 1 mm³ × 1 mm³ × 1 mm³, 188 sagittal slices, and acquisition time = 296 s. Precautions were provided for noise attenuation, and a birdcage head coil with foam padding was placed around the subject's head to minimize movement. The subjects were instructed to remain motionless and close their eyes during scanning.

MRI processing

Before processing the structural MR data, we visually inspected the MR images of all the subjects and excluded those of three participants with schizophrenia because of motion artifacts. Finally, structural T1 images of 57 schizophrenia patients and 18 healthy controls were converted to the NIfTI format using dcm2nii software[27] and then processed using FreeSurfer version 5.0 (<https://surfer.nmr.mgh.harvard.edu/>). The reconstruction of the cortical surface was performed using a standard automatic reconstruction algorithm, which generated several types of brain morphological features, including cortical volume (CV), cortical thickness (CT), and cortical surface area (CSA). Each feature was calculated for 34 brain regions for each hemisphere according to the Desikan-Killiany-Atlas[28].

Feature selection

When the CV, CT, and CSA features of 68 cortical regions were analyzed simultaneously, some uninformative, irrelevant, or redundant features could not be removed, leading to multicollinearity between features. Eliminating redundant features not only highlights important features but also improves classification accuracy. This study adopted the least absolute shrinkage and selection operator (LASSO) to address multicollinearity by compressing the coefficients of these unimportant variables to 0 and achieve feature selection.

Development and performance of the models

The establishment and evaluation of the models were conducted in R software. All the data were randomly divided into training (70%) and testing sets (30%). The training set was used for developing the models, and the testing set was used for assessing the performance of the models. Furthermore, to adjust the model parameters and avoid model overfitting, 10-fold cross-validation was performed on the training set. In 10-fold cross-validation, the entire dataset in the training set was randomly divided into 10 equal subsets. One subset was selected to test the model, and the remaining 9 subsets were used for training. This process was repeated 10 times. All algorithms were evaluated on the testing set using the area under the receiver operating characteristic curve (AUC) as a performance metric, and the algorithms were then compared to select the optimal one. An AUC of 0.5 indicates no discriminative ability, and 0.7-0.8 indicates good discrimination.

Statistical analysis

Statistical analysis was conducted in SPSS version 16.0. Differences in age, whole-brain volume and brain morphological features between schizophrenia patients and healthy controls were determined using *t* tests. *P* < 0.05 was considered to indicate statistical significance.

RESULTS

Comparison of demographic characteristics

There were no significant differences in age or whole-brain volume between male patients with schizophrenia and healthy controls, as shown in Table 1.

Selection of the important features

The important features selected by LASSO are shown in Table 2, including the banks of the superior temporal sulcus (bankssts), cuneus, inferior temporal, isthmus cingulate, lateral occipital, lingual, paracentral, parsopercularis, superior frontal, temporal pole, and insula cortex regions.

Table 1 Comparison of age and whole volume between two groups

Variables	Healthy controls	Schizophrenia patients	t value	P value
Age (yr)	34.06 ± 8.88	35.04 ± 11.21	-0.338	0.736
Whole volume (mm ³)	1203600.00 ± 88093.08	1164100.00 ± 112071.00	1.365	0.176

Table 2 The important features extracted by least absolute shrinkage and selection operator

Variables	Coefficients
Surface area	Bankssts
	Inferior temporal
	Lateral occipital
	Lingual
	Insula
	Isthmus cingulate
	Paracentral
Gray matter volume	Superior frontal
	Temporal pole
Cortical thickness	Lingual
	Cuneus
	Lateral occipital
	Par sopercularis

Comparison of features between groups

After the important features were selected using LASSO, we compared differences in these features between groups. Patients with schizophrenia showed reductions in the left bankssts area, left inferior temporal area, left lateral occipital area and left superior frontal volume as well as increased cortical thickness in the left lingual, right cuneus and lateral occipital regions compared with healthy controls, as shown in Table 3.

Performance of models

RF outperformed the other machine learning algorithms and achieved better classification performance, with an AUC of 0.886, as shown in Table 4. Subsequently, CV, CT, and CSA were used for the development of classification models using the RF algorithm. Among the three brain morphological features, CT performed best, and its AUC and balanced accuracy reached 0.605, as shown in Table 5.

DISCUSSION

In the present study, we employed the important features extracted from several brain morphological features using LASSO and *t* tests, including CV, CT, and CSA, to establish models for the classification of male schizophrenia patients and healthy controls based on four commonly used machine learning algorithms, namely, GLM, RF, KNN, and SVM, and then compared the classification performance of these models in terms of AUC to determine the optimal machine learning algorithm.

In this study, there were a total of 8 morphological features with significant differences between groups, including the left bankssts CSA, right cuneus CT, left inferior temporal CSA, left lateral occipital CSA, left lingual CT, left superior frontal CV, right cuneus CT, and right lateral occipital CT, which are largely consistent with the findings of many previous studies. For example, Shi *et al*[29] reported abnormalities in the inferior temporal gyrus and superior frontal gyrus. Zhao *et al*[30] reported that schizophrenia patients had extensive structural abnormalities, such as in the occipital lobe and superior frontal gyrus. These results suggest extensive changes in the brains of schizophrenia patients, which may be important regions in the classification of schizophrenia patients and healthy controls.

We found that RF performed better (with an AUC of 0.886) in discriminating male schizophrenia patients from healthy controls than did the other three machine learning algorithms, which was consistent with the results of other studies[14, 24]. Furthermore, the RF algorithm identified as the best algorithm in this study had higher classification accuracy than those of previous studies[31]. For example, a study utilizing SVM with gray matter and white matter features selected

Table 3 Comparison of morphological features between two groups

Variables	Schizophrenia patients	Healthy controls	t value	P value
Left bankssts area	1016.20 ± 170.13	1133.20 ± 186.00	-2.488	0.015
Left inferior temporal area	3492.30 ± 557.45	3856.30 ± 423.39	-2.544	0.013
Left lateral occipital area	4925.30 ± 719.19	5489.80 ± 480.09	-3.111	0.003
Left lingual area	2812.00 ± 444.30	3236.70 ± 479.05	-3.471	0.001
Left lingual thickness	2.08 ± 0.17	1.99 ± 0.10	2.121	0.037
Left superior frontal volume	23123.00 ± 2824.16	24744.00 ± 2448.14	-2.187	0.032
Right cuneus thickness	2.01 ± 0.14	1.89 ± 0.14	2.938	0.004
Right lateral occipital thickness	2.18 ± 0.15	2.07 ± 0.15	2.738	0.008

Table 4 Performance of each machine learning algorithm

Algorithms	AUC	Balanced accuracy, %	Sensitivity	Specificity
GLM	0.728 (0.470-0.986)	61.84	0.737	0.500
RF	0.886 (0.754-1.000)	64.04	0.947	0.333
KNN	0.601 (0.257-0.945)	55.70	0.947	0.167
SVM	0.842 (0.670-1.000)	50.00	1.000	0.000

AUC: Area under receiver operating characteristic curves; GLM: General linear model; RF: Random forest; KNN: K-nearest neighbor; SVM: Support vector machine.

Table 5 The performance for each structural feature

Features	AUC	Balanced accuracy, %	Sensitivity	Specificity
Surface area	0.474 (0.241-0.706)	39.50	0.789	0.000
Gray matter volume	0.553 (0.235-0.871)	56.60	0.632	0.500
Cortical thickness	0.605 (0.327-0.884)	55.70	0.947	0.167

AUC: Area under receiver operating characteristic curves.

with recursive feature elimination to discriminate individuals with schizophrenia from healthy controls reported that the optimal machine learning algorithm achieved an accuracy of over 85% [19]. In another study, features selected from amygdaloid and hippocampal subregions using sequential backward elimination were employed to distinguish between schizophrenia patients and normal controls, and the SVM classifier achieved an accuracy of 81.75% [24]. Yassin *et al* [21] used subcortical volumes and cortical thickness features of 64 schizophrenia patients and 106 healthy controls, and the RF classifier applied to subcortical volumes had the highest accuracy of 76.4%. Xiao *et al* [23] used cortical thickness and CSA data to classify 163 schizophrenia patients and 163 healthy controls and achieved accuracies ranging from 81%-85%. In another study using a diverse set of neuroanatomical measures and ensemble methods, the classification accuracies of the ensemble methods ranged from 83% to 87% [20]. In addition, compared to other brain morphological features, the classification model established using RF and CT achieved greater classification accuracy, which is consistent with results from previous studies reporting that cortical thickness features yielded greater classification performance than other neuroanatomical features [14,21]. The higher performance of the classification models in this study compared with those in other studies may be due to the following reasons. First, LASSO was adopted for the selection of important features in our study. All brain morphology features were ranked according to their importance, and the unimportant features were filtered out. This not only increases the computation speed but also improves the accuracy of classification [32]. Second, we employed more brain morphological indices as input features for classification than did other studies. Finally, due to the close association of the type of data with the performance of each machine learning method, we compared the performance of several machine learning algorithms in discriminating schizophrenia patients from normal controls and found that RF performed best, suggesting that RF is more appropriate for brain morphological features extracted using LASSO. Additionally, RF is regarded as an ensemble method that can combine individual weak classifiers to generate a more robust classification system.

Several limitations in this study need to be considered. First, the size of the sample was relatively small. Future studies should recruit more subjects to improve the ability to classify patients with schizophrenia and healthy controls. Second, validation data from another center were not available, which impacted the generalizability of the classification models. Future research should perform external validation at other sites. Third, the schizophrenia patients included in this study had chronic schizophrenia, and their brain structures could have been influenced by antipsychotic use. Future studies should be conducted in first-episode, medication-naïve patients with schizophrenia to validate our results.

CONCLUSION

In this study, we found structural abnormalities in some brain regions primarily involved in the temporal and frontal lobes in schizophrenia patients. Compared with other algorithms, RF showed better performance in discriminating male schizophrenia patients from healthy controls.

ACKNOWLEDGEMENTS

The authors thank all participants in the study, as well as investigators involved in conducting the study.

FOOTNOTES

Author contributions: Yu T designed the study, analyzed the data, and wrote the manuscript; Pei WZ collected the relevant data; Zhang XL provided financial support; Xu CY provided technological support; Deng CC edited the manuscript; and all authors have read and approved the final manuscript.

Supported by the University Research Fund of Anhui Medical University, No. 2022xkj119.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Fourth People's Hospital of Hefei [Approval No. HFSY-IRB-YJ-KYXM-YT (2024-003-001)].

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

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

Data sharing statement: Data used in this study can be available from the corresponding author at 479800330@qq.com.

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

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S-Editor: Chen YL

L-Editor: A

P-Editor: Che XX

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Retrospective Study

Assessing the current situation and the influencing factors affecting perceived stigma among older patients after leukemia diagnosis

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C

Novelty: Grade B, Grade C

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade B, Grade B

P-Reviewer: De Molina JA, Singapore; Uddin M, Saudi Arabia

Received: February 20, 2024

Revised: April 13, 2024

Accepted: April 25, 2024

Published online: June 19, 2024

Processing time: 120 Days and 6.4 Hours



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Abstract

BACKGROUND

Psychological problems are becoming increasingly prominent among older patients with leukemia, with patients potentially facing stigmatization after diagnosis. However, there is limited research on the stigma experienced by these patients and the factors that may contribute to it.

AIM

To investigate the stigma faced by older patients after being diagnosed with leukemia and to analyze the potential influencing factors.

METHODS

A retrospective analysis was conducted using clinical data obtained from questionnaire surveys, interviews, and the medical records of older patients with leukemia admitted to the Hengyang Medical School from June 2020 to June 2023. The data obtained included participants' basic demographic information, medical history, leukemia type, family history of leukemia, average monthly family income, pension, and tendency to conceal illness. The Chinese versions of the Social Impact Scale (SIS), Perceived Social Support Scale (PSSS), Self-Rating Anxiety Scale (SAS), and Self-Rating Depression Scale (SDS) were used to assess indicators related to stigma, social support, and mental health status. We used Pearson's correlation coefficient to analyze the strength and direction of the relationship between the scores of each scale, and regression analysis to explore the factors related to the stigma of older patients with leukemia after diagnosis.

RESULTS

Data from 120 patients with leukemia aged 65-80 years were analyzed. The total

score on the SIS and PSSS was 43.60 ± 4.07 and 37.06 ± 2.87 , respectively. The SAS score was 58.35 ± 8.32 and the SDS score was 60.58 ± 5.97 . The stigma experienced by older leukemia patients was negatively correlated with social support ($r = -0.691$, $P < 0.05$) and positively correlated with anxiety and depression ($r = 0.506$, 0.382 , $P < 0.05$). Age, education level, smoking status, average monthly family income, pension, and tendency to conceal illness were significantly associated with the participants' level of stigma ($P < 0.05$). Age, smoking status, social support, anxiety, and depression were predictive factors of stigmatization among older leukemia patients after diagnosis (all $P < 0.05$), with a coefficient of determination (R^2) of 0.644 and an adjusted R^2 of 0.607.

CONCLUSION

Older patients commonly experience stigmatization after being diagnosed with leukemia. Factors such as age, smoking status, social support, and psychological well-being may influence older patients' reported experience of stigma.

Key Words: Senile leukemia; Stigma; Social support; Anxiety; Depression; Influencing factors

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Core Tip: The most innovative and important finding of this study is that older patients with leukemia commonly experience feelings of stigmatization after diagnosis, which are influenced by factors such as age, smoking status, social support, and psychological status. This study highlights the importance of addressing the psychological well-being and social support that older patients with leukemia receive to mitigate feelings of stigmatization and to improve their overall quality of life.

Citation: Tang X, Chen SQ, Huang JH, Deng CF, Zou JQ, Zuo J. Assessing the current situation and the influencing factors affecting perceived stigma among older patients after leukemia diagnosis. *World J Psychiatry* 2024; 14(6): 812-821

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/812.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.812>

INTRODUCTION

The data obtained for this study show that the incidence rate of leukemia in China is currently 6.21 per 100000, with a mortality rate of 4.03 per 100000[1]. The age of China's population is increasing, with over 267 million Chinese citizens currently aged 60 and above. The number of older patients with acute leukemia is also increasing annually[2], making them the core demographic among adults diagnosed with acute leukemia. A leukemia diagnosis is a major blow to patients. Leukemia not only affects patients' physical health, but it can also cause psychological and social problems. Among the range of potential side effects that follow a leukemia diagnosis, stigma is a common psychological reaction. Stigma refers to the embarrassment or self-doubt that patients often experience in relation to their illness[3,4]. It is a complex issue involving multiple disciplines, including medicine, sociology, and psychology, and has received increasing attention from researchers in recent years.

Extensive research has been conducted into the stigma that occurs around certain diseases such as human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS) and mental illnesses. In a study by Vrbova *et al*[5], patients with stable schizophrenia revealed a tendency to choose suicide as a means of escaping the psychological problems they faced, with the increased stigma caused by the illness putting them at greater risk of committing suicide. Clement *et al*[6] conducted a systematic review of 144 studies on stigma among mental health patients. Their findings revealed the mild-to-moderate impact of stigma on patients' likelihood of seeking help, with disclosure of the problem being the most common stigma barrier. Nikus Fido *et al*[7] found that HIV/AIDS patients commonly experience stigma, with educational level and gender being closely related to stigma, and social support being an important influencing factor. Studies have found that stigma can lead to a delay in seeking medical treatment, concealment of disease information, avoidance of social activities, and reduced treatment adherence, thereby affecting patients' recovery and quality of life[8,9]. Stigma can cause older patients with leukemia to experience self-denial, confusion, and helplessness. It can also lead to self-isolation and avoidance of interactions with the outside world, depriving patients of opportunities to connect with family, friends, and other patients with similar experiences, further increasing their emotional burden. These emotional issues can also impact patients' immune systems, making them more susceptible to infection and making their recovery more difficult, thus creating a vicious cycle.

Psychological problems among older patients with leukemia are becoming increasingly prominent. However, limited research has been conducted on the role that stigma plays with regard to these issues. Understanding and recognizing whether older patients experience stigma after being diagnosed with leukemia and conducting in-depth research on the factors that influence stigma can help facilitate the development of more effective methods and strategies. These strategies can in turn help to alleviate the symptoms associated with stigma and enable patients to cope more easily, allowing for more comprehensive support and assistance to be provided to them.

MATERIALS AND METHODS

Patient characteristics

The dataset for this retrospective analysis was derived from clinical data, such as questionnaires, interviews, and medical records filled in by older patients with leukemia admitted to the Hengyang Medical School, University of South China from June 2020 to June 2023. To ensure the consistency and comparability of the subjects, it was necessary to develop inclusion criteria through which to screen patients and determine if they met the requirements of the study. The inclusion criteria were as follows: (1) Patients had been diagnosed with leukemia for the first time and were over 65 years of age, regardless of sex, race, or disease type; and (2) patients were willing to participate in the study and capable of providing informed consent. Patients who did not fit the study's criteria, or whose condition may have interfered with the results of the study, such as patients with cognitive impairment or severe mental illness, patients with other major diseases or complications, or patients who could not provide valid data were all excluded from participating.

Method

Demographic factors relating to age, sex, marital status, education level, smoking and drinking status, underlying medical history, average monthly family income, retirement pension, type of leukemia, family history of leukemia, and tendency to conceal disease were obtained from the questionnaire survey records. Patients' reported levels of stigma, social support, and psychological well-being were assessed using Chinese versions of the Social Impact Scale (SIS), Perceived Social Support Scale (PSSS), Self-Rating Anxiety Scale (SAS), and Self-Rating Depression Scale (SDS). The dimensions and scoring methods of these scales are as follows: (1) The SIS consists of 18 items and three dimensions (social rejection, social isolation, and internal stigma). A 4-point Likert scale was used for each item, with responses ranging from "1-strongly disagree" to "4-agree." The total score ranged from 18-72 points, with higher scores indicating a higher level of stigma experienced by patients; (2) the PSSS consists of 12 items and three dimensions (family, friends, and other support). A 7-point Likert scale was used for each item, with responses ranging from "1-strongly disagree" to "7-agree." The total score ranged from 12-84 points, with higher scores indicating better perceived support; and (3) the SAS and SDS each contained 20 questions covering psychological and physiological symptoms of anxiety and depression, such as tension, fear, and worry. A 4-point Likert scale was used for each question, with responses ranging from "1-none or rarely" to "4-frequently or almost always". The total score ranged from 20-80 points, with higher scores indicating more severe anxiety and depression symptoms.

Missing data processing

To minimize the impact of missing data on the results, the following methods were adopted: (1) During data collection, the collected data were carefully examined to ensure optimal data integrity and accuracy; (2) the reasons for any missing data, such as questionnaire errors or losses, were carefully analyzed to ensure that appropriate measures were taken; and (3) for partially missing data, imputation methods such as mean and multiple imputations were employed to handle data filling.

Statistical analysis

The means and standard deviations were calculated to describe the average scores for each scale. Percentages or frequencies were used to determine the proportion or frequency of individuals with different score ranges. Significant differences in scores between different groups (*e.g.*, sex and age groups) were compared using the *t*-test or analysis of variance (ANOVA) and multiple comparisons were made using the Fisher's least significant difference test. The relationship between the scale scores and other variables was analyzed using Pearson's correlation. A regression analysis was then conducted to predict the relationship between the scale scores and independent variables. All analyses were performed using SPSS 23.0, with a significance level of $\alpha = 0.05$.

RESULTS

Clinical characteristics

After the screening was completed, 120 patients aged 65-80 years were enrolled. The majority of the patients had been diagnosed with acute leukemia, of whom 89 (74.2%) reported having no family history of leukemia. The patients' education level was roughly balanced: 33 patients (27.50%) had a junior high school level education or below, 44 patients (36.67%) had a senior high school/technical secondary school level education, and 43 patients (35.83%) had a college level education or above. In terms of bad habits, 42 patients (35%) smoked and 69 (57.50%) consumed alcohol. The proportion of patients with a per capita monthly family income of 3000-5000 yuan was the largest, accounting for 49 cases (40.83%), while more than half of the patients reported having no pension (Table 1).

Stigma

The score for the social exclusion dimension was 13.82 ± 2.41 ; the score for the social isolation dimension was 7.32 ± 1.33 ; the score for the internal stigma dimension was 22.47 ± 2.97 , and the SIS-total score was 43.60 ± 4.07 . These results suggest that patients may face exclusion and isolation from society and may internalize a strong sense of stigma in relation to the disease (Table 2).

Table 1 General demographic data of older patients with leukemia

Items	Groups	Frequency	%
Age (yr)	65-75	50	41.7
	> 75	70	58.3
Sex	Male	53	44.2
	Female	67	55.8
Marital status	Single	6	5.0
	Married	89	74.2
	Divorced/widowed	25	20.8
Education level	Junior high school and below	33	27.5
	High school or technical secondary school	44	36.7
	College or above	43	35.8
Smoking	No	78	65.0
	Yes	42	35.0
Drinking	No	51	42.5
	Yes	69	57.5
Medical history	No	62	51.7
	Yes	58	48.3
Average monthly family income (CNY)	< 3000	29	24.2
	3000-5000	49	40.8
	> 5000	42	35.0
Pension	No	67	55.8
	Yes	53	44.2
Leukemia type	Chronic	34	28.3
	Acute	86	71.7
Family history	No	89	74.2
	Yes	31	25.8
Tendency to conceal illness	No	47	39.2
	Yes	73	60.8

Table 2 Social Impact Scale score

Scale	Item	Score range	Score
Social exclusion dimension	7	7-28	13.82 ± 2.41
Social isolation dimension	3	3-12	7.32 ± 1.33
Internal shame dimension	8	8-32	22.47 ± 2.97
SIS-total	18	18-72	43.60 ± 4.07

SIS: Social Impact Scale.

Social support, mental health status

The score for the family support dimension was 14.23 ± 1.83 ; the score for the friend support dimension was 12.05 ± 1.53 ; the score for the other support dimension was 10.78 ± 1.91 ; and the PSSS-total score was 37.06 ± 2.87 . The SAS score was 58.35 ± 8.32 points, and the SDS score was 60.58 ± 5.97 points. These results suggest that older patients with leukemia experience a moderate level of support from family, friends, and others, and that the overall level of social support they receive is relatively low. However, the scores corresponding to anxiety and depression in the patients' self-evaluation

were also higher, meaning further attention and intervention are needed (Table 3).

Single factor analysis of stigma

The classification of different demographic and disease-related data variables were used as independent variables, and stigma was used as the dependent variable for a single-factor analysis. There were statistically significant differences in patients' age, education level, smoking status, family monthly income per capita, pension, and disease concealment tendency ($P < 0.05$) (Table 4).

Correlation analysis

Pearson's correlation analysis showed that social support was negatively correlated with stigma ($r = -0.691$, $P < 0.05$), and anxiety and depression were positively correlated with stigma ($r = 0.506$, 0.382 , $P < 0.05$) as shown in Figure 1.

Multiple linear regression analysis

Stigma was used as the dependent variable, and the variables of age, education level, smoking status, family monthly income per-capita, pension, disease concealment tendency, social support, anxiety, and depression were all subjected to regression analysis. A normality test was performed during the analysis, as was a residual analysis of the fitted model. The residuals followed a normal distribution. The assignments of each variable and dummy variable are presented in Table 5.

Before entering the regression equation, the variables were subjected to a multicollinearity diagnosis. The variance inflation factor ranged from 1.095 to 1.469, suggesting that the respective variables had no collinearity problems and could be subjected to regression analysis. The results showed that age, smoking status, social support, anxiety, and depression entered the linear regression equation and were predictors of stigma in older patients after leukemia diagnosis (all $P < 0.05$). The determination coefficients were $R^2 = 0.644$ and the adjusted $R^2 = 0.607$ (Table 6).

DISCUSSION

The scores for the three dimensions of SIS were 13.82 ± 2.41 points, 7.32 ± 1.33 points, and 22.47 ± 2.97 points, with a total score of 43.60 ± 4.07 points. This suggests that older patients with leukemia may face social exclusion and isolation and may also experience strong feelings of stigma and disease-related stigma. This may be attributable to several factors, the first of which is social cognition and prejudice. Leukemia is considered to be a serious disease that is strongly associated with death. Therefore, patients may feel themselves labeled as being "sick," and may subsequently face discrimination and exclusion from society. Social cognition and prejudice can lead to feelings of stigma and embarrassment[10]. The second potential reason concerns the discomfort and side effects that result from leukemia treatment. Leukemia treatment, which can include chemotherapy, radiation therapy, and bone marrow transplantation, is often a challenging process[11,12]. These treatments can produce side effects and physical discomfort, for example, nausea, hair loss, and fatigue. Patients anticipate experiencing physical image barriers and declining bodily functions, which can lead to feelings of stigma and embarrassment, further intensifying their sense of stigma. Finally, older leukemia patients experience significant changes in terms of their quality of life. The diagnosis and treatment of leukemia can have a significant impact on patients' lives. Patients may require frequent medical checkups and treatments that disrupt and limit their daily lives. In Chinese culture, family expectations and pressures have a significant influence on individuals [13]. These changes may cause patients to feel a sense of shame and to lose their self-esteem, leading to further stigmatization. Hence, similarly to the results recorded in previous studies[5-7], most patients in this study reported experiencing varying levels of stigma. A study of patients with different types of cancer found that disease-related stigma was prevalent and was associated with factors such as sex, age, education level, and level of social support[14]. Our findings also indicated that the level of stigma experienced by older leukemia patients was comparatively lower than that of breast cancer patients (55.20 ± 12.15 points)[15] and oral cancer patients (50.17 ± 21.24 points)[16]. This may be related to societal cognition and acceptance, changes in appearance and image, and the influence of sex and gender roles.

The formation of disease-related stigma is complex and involves factors such as negative social evaluation, patients' own lack of understanding, personality traits, family support, and societal care. One study found that stigma in cancer patients was related to the personality traits of individual patients, with patients with more introverted, neurotic, and depressive tendencies being more prone to experiencing disease-related stigma[17]. Another study found that family support and societal care significantly alleviated patients' disease-related stigma, improved their quality of life, and enhanced their psychological well-being[18].

The correlation analysis conducted in this study further supported these findings, revealing a positive correlation between anxiety, depression, and disease-related stigma and a negative correlation between social support and disease-related stigma. Anxiety and depression can make patients feel discouraged and hopeless, and cause them to engage in self-blame with regard to their illness, thereby exacerbating disease-related stigma[19]. These negative emotions can make patients overly sensitive to judgment and criticism from others, further deepening their sense of perceived stigmatization. Social support can provide emotional and informational support as well as practical assistance[20,21]. Together, this can help patients to cope with the difficulties and challenges that accompany a leukemia diagnosis and the resulting treatment. Such support can decrease feelings of loneliness, helplessness, and self-blame, thereby reducing disease-related stigma.

Table 3 Perceived Social Support Scale, Self-Rating Anxiety Scale, and Self-Rating Depression Scale scores

Scale	Item	Score range	Score
Family support dimension	4	4-28	14.23 ± 1.83
Friend support dimension	4	4-28	12.05 ± 1.53
Other support dimension	4	4-28	10.78 ± 1.91
PSSS-total	12	12-84	37.06 ± 2.87
SAS-total	20	20-80	58.35 ± 8.32
SDS-total	20	20-80	60.58 ± 5.97

PSSS: Perceived Social Support Scale; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale.

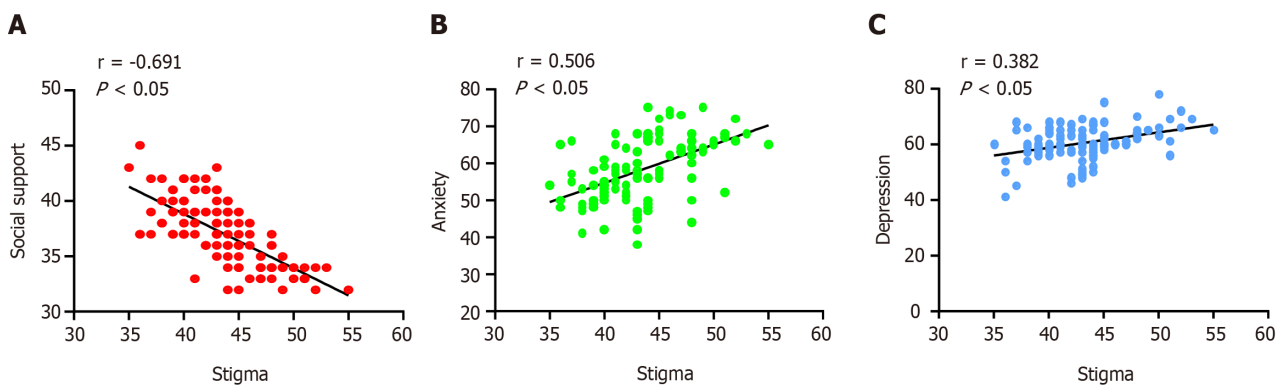


Figure 1 Correlation analysis of patients' reported experience of stigma alongside social support, anxiety, and depression. A: Social support; B: Anxiety; C: Depression.

Linear regression analysis revealed that both age and smoking status were predictors of stigmatization in older patients with leukemia after diagnosis. Among these factors, age may have the greatest impact on stigma in older patients with leukemia. Liu *et al*[22] also emphasized this point in their study on the stigma experienced by patients with lung cancer. Leukemia treatment often requires significant medical resources and financial investment[23,24]. Thus, patients may be concerned that their illness will impose a burden on their families and society as a whole in terms of medical resources and finances. Older patients may also feel that they should be enjoying retirement and a peaceful life rather than facing a serious illness. It is worth noting that only 35.00% of patients reported having a monthly household income in excess of 5000 yuan, and that 55.83% of patients reported not having a pension, both of which are strong indicators of economic difficulties. Additionally, older adults may have limited knowledge and information about leukemia, which can create more doubts and anxieties about the disease, thereby increasing older patients' perception of disease-related stigma. Smoking is an unhealthy lifestyle habit that may be associated with an increased risk of developing leukemia[25, 26]. Upon being diagnosed with leukemia, patients may perceive their smoking habit to be one of the causes of their disease, leading to guilt and self-blame, which can further exacerbate their perception of disease-related stigma. In this study, social support, anxiety, and depression were identified as predictive variables. Social support had a positive impact on reducing stigma among older patients with leukemia, whereas anxiety and depression had the opposite effects. As mentioned earlier, social support can be further categorized as being instrumental or emotional[20,21], with both forms of support being crucial for patients. Patients who lack social support may feel more isolated and ashamed. Negative emotions, such as anxiety and depression, can increase patients' level of self-denial and perception of stigma regarding their condition.

A number of coping strategies can be proposed in response to the factors identified as influencing disease-related stigma in older patients with leukemia. Providing detailed information and knowledge about leukemia to older patients, such as by emphasizing that the development of leukemia is not solely related to smoking but also to other genetic, environmental, and health factors may help to reduce patients' excessive self-blame for their smoking behavior and decrease their associated disease-related stigma. Establishing good communication and trust with patients, listening to their concerns and the emotions they are experiencing, and providing appropriate psychological support are other useful coping strategies. This can include providing emotional support, guiding patients to seek professional psychological counseling, or encouraging them to join support groups. Helping patients to find and join relevant leukemia support groups or organizations can also enable them to share their experiences and to receive emotional support from other patients. Finally, patients can communicate with their families and social organizations to seek economic support and assistance. Medical expenses and insurance matters should be discussed simultaneously with the relevant healthcare team to assist in alleviating patients' financial burden.

Table 4 Univariate analysis

Variable	<i>n</i>	SIS-total	<i>t/F</i>	<i>P</i> value
Age (a)			-4.006	< 0.05
65-75	50	41.94 ± 3.61		
> 75	70	44.79 ± 3.99		
Sex			-1.030	0.305
Male	53	43.17 ± 3.78		
Female	67	43.94 ± 4.29		
Marital status			1.053	0.352
Single	6	42.00 ± 3.90		
Married	89	43.90 ± 4.28		
Divorced/widowed	25	42.92 ± 3.23		
Education level			4.231	0.017 ¹
Junior high school and below	33	42.37 ± 3.27		
High school or technical secondary school	44	43.73 ± 3.94		
College or above	43	45.03 ± 4.75		
Smoking			-3.865	< 0.05
No	78	42.60 ± 3.81		
Yes	42	45.45 ± 3.93		
Drinking			-1.393	0.166
No	51	43.00 ± 3.82		
Yes	69	44.04 ± 4.22		
Medical history			0.259	0.796
No	62	43.69 ± 4.40		
Yes	58	43.50 ± 3.72		
Average monthly family income (CNY)			4.522	0.013 ¹
< 3000	29	42.48 ± 3.81		
3000-5000	49	43.53 ± 3.72		
> 5000	42	45.34 ± 4.51		
Pension			3.176	0.002
No	67	44.61 ± 4.25		
Yes	53	42.32 ± 3.47		
Leukemia type			0.675	0.501
Chronic	34	44.00 ± 3.87		
Acute	86	43.44 ± 4.16		
Family history			0.286	0.776
No	89	43.66 ± 4.23		
Yes	31	43.42 ± 3.64		
Tendency to conceal illness			-2.154	0.033
No	47	42.62 ± 3.72		
Yes	73	44.23 ± 4.19		

¹The multiple comparison result of the least significant difference test. Patients' reported history of underlying diseases refers to diseases such as diabetes,

hypertension, and hyperlipidemia. SIS: Social Impact Scale.

Table 5 Independent variable and dummy variable assignment method

ID	Variable	Assignment
X01	Age (a)	0 = 65-75, 1 \geq 75
X02	Education level	Junior high school and below ($Z_1 = 0, Z_2 = 0, Z_3 = 0$); High school or technical secondary school ($Z_1 = 0, Z_2 = 1, Z_3 = 0$); College or above ($Z_1 = 0, Z_2 = 0, Z_3 = 1$)
X03	Smoking	0 = No, 1 = Yes
X04	Average monthly family income (CNY)	> 5000 ($Z_1 = 0, Z_2 = 0, Z_3 = 0$); 3000-5000 ($Z_1 = 0, Z_2 = 1, Z_3 = 0$); < 3000 ($Z_1 = 0, Z_2 = 0, Z_3 = 1$)
X05	Pension	0 = No, 1 = Yes
X06	Tendency to conceal illness	0 = No, 1 = Yes
X07	Social support	Actual measuring
X08	Anxiety	Actual measuring
X09	Depression	Actual measuring

Table 6 Multivariate linear regression analysis

Variable	Group	β	SE	β'	t	P value
Constant		55.607	5.278	—	10.535	< 0.05
Age (a)		1.442	0.494	0.175	2.918	0.004
Education level	Junior high school and below	0.604	0.632	0.066	0.955	0.342
	High school or technical secondary school	0.227	0.572	0.027	0.396	0.693
Smoking		1.479	0.533	0.174	2.775	0.007
Average monthly family income (CNY)	< 3000	0.938	0.654	0.099	1.433	0.155
	3000-5000	0.531	0.565	0.064	0.940	0.349
Pension		-0.160	0.514	-0.02	-0.311	0.757
Tendency to conceal illness		0.885	0.514	0.107	1.721	0.088
Social support		-0.670	0.097	-0.472	-6.873	< 0.05
Anxiety		0.079	0.034	0.162	2.351	0.021
Depression		0.093	0.043	0.137	2.192	0.031

$R = 0.802$, $R^2 = 0.644$, $\Delta R^2 = 0.607$, $F = 17.733$, $P < 0.05$.

Advantages and limitations

This study has the following advantages: (1) It considers multiple factors that may influence patients' perceived sense of stigmatization, including age, smoking status, alcohol consumption, average monthly household income, pension, tendency to conceal illness, level of social support, anxiety, and depression. This enables us to develop a more comprehensive understanding of the impact of these factors on patients' sense of stigmatization; (2) this study included older patients with leukemia from various socioeconomic backgrounds and age groups, thereby improving the overall representativeness and generalizability of the study results; and (3) this study identified a number of coping strategies for helping patients to deal with their own sense of stigmatization. These strategies can provide practical assistance and guidance to patients. However, the study also has some notable limitations: (1) The study only included specific types of older leukemia patients from specific regions, so the results may not be generalizable; and (2) the assessment of stigma in this study may have been based on patients' own subjective feelings, as the study lacked more objective indicators or measurement tools.

CONCLUSION

Older patients with leukemia may experience strong feelings of stigmatization and disease-related stigma influenced by various factors. By gaining a deeper understanding of the formation of and factors influencing disease-related stigma, we can provide more comprehensive and effective psychological support and interventions for older patients. The results of this study also contribute to raising awareness and understanding of older patients with leukemia among healthcare teams and the public in general, promoting the need for greater social support and assistance.

FOOTNOTES

Author contributions: Tang X designed and performed the study and wrote the manuscript; Chen SQ and Zuo J provided clinical advice and supervised this study; Huang JH provided psychological adjustment and health education to patients; Deng CF and Zou JQ collected questionnaires and contributed to the analysis.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Hengyang Medical School, University of South China.

Informed consent statement: All study participants or their legal guardians provided written informed consent for personal and medical data collection prior to their enrolment in the study.

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

Data sharing statement: The data used in this study can be obtained from the corresponding author upon request.

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S-Editor: Qu XL

L-Editor: A

P-Editor: Che XX

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Retrospective Study

Status quo and factors of depression and anxiety in patients with non-muscle invasive bladder cancer after plasma electrocision

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade B, Grade B

P-Reviewer: Elbeddini A, Canada; Frost C, United Kingdom

Received: February 22, 2024

Revised: April 9, 2024

Accepted: April 30, 2024

Published online: June 19, 2024

Processing time: 118 Days and 11.1 Hours



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Abstract

BACKGROUND

Bladder cancer is a type of cancer with a high incidence in men. Plasma electro-surgery (PES) is often used in the treatment of bladder cancer. Postoperative complications often cause depression and anxiety in patients after surgery.

AIM

To investigate the current state of depression and anxiety after PES in patients with non-muscle-invasive bladder cancer and analyze the factors affecting them.

METHODS

A retrospective study was conducted to compare the baseline data of patients by collecting their medical history and grouping them according to their mental status into negative and normal groups. Logistic regression analysis was used to explore the risk factors affecting the occurrence of anxiety and depression after surgery in patients with bladder cancer.

RESULTS

Comparative analyses of baseline differences showed that the patients in the negative and normal groups differed in terms of their first surgery, economic status, educational level, and marital status. A logistic regression analysis showed that it affected the occurrence of anxiety in patients with bladder cancer, and the results showed that whether the risk factors were whether or not it was the first surgery, monthly income between 3000 and 3000-6000, secondary or junior high school education level, single, divorced, and widowed statuses.

CONCLUSION

The risk factors affecting the onset of anxiety and depression in bladder cancer

patients after PES are the number of surgeries, economic status, level of education, and marital status. This study provides a reference for the clinical treatment and prognosis of bladder cancer patients in the future.

Key Words: Bladder cancer; Anxiety; Depression; Analysis of influencing factors; Plasma electrocision

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Core Tip: This study provides a theoretical basis for the clinical treatment and rehabilitation of bladder cancer patients. In the future, we should pay more attention to the mental health status of bladder cancer patients and their risk factors in order to provide more comprehensive and effective treatment and rehabilitation programmes.

Citation: Lu B, Ding M, Xu HB, Yan CY. Status quo and factors of depression and anxiety in patients with non-muscle invasive bladder cancer after plasma electrocision. *World J Psychiatry* 2024; 14(6): 822-828

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/822.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.822>

INTRODUCTION

Bladder cancer is a malignant tumor of the bladder mucosa[1]. It is the most common malignant tumor of the urinary system. The latest statistics show that the incidence rate of bladder cancer has shown a significant rising trend, with men being the main group with bladder cancer[2]. Bladder cancer is a type of malignant tumor with a high recurrence rate, and the factors that cause its onset are more complicated, including intrinsic genetic and extrinsic environmental factors [3]. In the modern clinical treatment of non-muscle invasive bladder cancer[4]. With the continuous progress of human civilization, the incidence of malignant bladder tumors has increased in China in recent years. Smoking, alcohol consumption, long-term exposure to chemical products, and occupational exposure to toxic substances are the main risk factors for malignant bladder tumors. In China, the population, especially the male population, has a significant impact on the incidence of malignant bladder tumors owing to the high rates of smoking and alcohol consumption[5].

The clinical treatment of bladder cancer mainly involves resection of tumor lesions, prevention of tumor recurrence, prevention of recurrent tumor progression, prolongation of patient survival time, and improvement of patient quality of life as the main objectives. Plasma electrosurgery (PES) is a common surgical treatment option. However, previous studies have shown that PES has some limitations. This procedure is prone to trigger an occlusive nerve reflex, resulting in bladder perforation, which requires a high level of skill on the part of the operator. Moreover, some patients show signs of urinary tract irritation, such as frequent urination and urgency after surgery. Second, because of the thermal cutting of electrodesiccation, the cut surface often forms a large number of scabs, postoperative edema, degeneration, or even necrosis of local tissues. If the ureteral orifice, the bladder neck, and its surrounding tissues are edematous and necrotic, it can be secondary to urinary obstruction, and necrotic tissues induce the body to produce inflammatory factors that can cause bladder irritation, such as frequency, urgency, and painful urination.

Previous studies have found that many cancer patients are prone to anxiety and depression during treatment[6]. About 15%-25% of patients with cancer suffer from comorbid depression each year, which is four times more prevalent than in the general population. Nearly 20% of cancer patients experience severe anxiety[7]. Depression in patients with cancer often has serious consequences, including treatment abandonment and suicide tendencies. Recent studies have identified depression as an independent risk factor for predicting mortality in patients with cancer[8,9]. However, the increased prevalence of depression is not solely caused by a single psychosocial stressor during cancer diagnosis. Surgical treatment modalities, prognostic outcomes, and financial stress are also major risk factors for comorbid depression in patients with cancer[10]. There is a lack of research exploring the factors influencing the occurrence of depression and anxiety after PES in patients with non-muscle invasive bladder cancer at this stage of the study.

This study uses a retrospective design by analyzing the incidence of depression and anxiety after PES in patients with non-muscle invasive bladder cancer. It clarifies the current status of the occurrence of depression and the factors influencing the occurrence of depression in patients with bladder cancer through the use of logistic regression. It shows that providing a scientific basis for the prevention and treatment of the occurrence of depression and anxiety in patients with bladder cancer and improving patient prognosis is possible.

MATERIALS AND METHODS

Researchers and study design

One hundred and twenty patients with bladder cancer who visited the Department of Urology between May 2020 and May 2023 and were diagnosed by two attending physicians were included in the main study population. The patients' medical history data were collected during the consultation period, their psychological status was assessed at the time of

discharge, and they completed the depression and anxiety scales to assess the occurrence of depression and anxiety.

The diagnostic criteria for bladder cancer were based on the Chinese Bladder Cancer Guidelines 2022 Edition, and the clinical diagnosis was made based on the patients' medical history, symptoms, and signs, combined with laboratory examination, imaging examination, urine cytology, urine tumor marker examination, and cystoscopy. Inclusion criteria of the study subjects: (1) Patients were clinically diagnosed as non-muscle invasive bladder cancer; (2) Preoperative urological imaging [ultrasound, plain computed tomography (CT) and enhanced CT, *etc.*] did not show any combination of urological, other primary or secondary tumors; (3) No lymph node metastasis or distant metastasis of tumor was seen; (4) Pathological staging of the patient's cancer was based on the classification of the bladder cancer according to the World Health Organization's Bladder Cancer Nausea Level Classification published in 2004. Uroepithelial cancer nausea grading system issued by the World Health Organization in 2004; and (5) Patients who had regular bladder perfusion therapy after surgery and received timely follow-up examinations on time; and patients who underwent cystoscopy for one year.

All the patients underwent PES. Treatment process: After anesthesia and truncl position, the perineum was routinely disinfected and towed, and the bladder was inserted smoothly under the direct vision of F25.6 circon-electrosurgical scope. After passing through, we saw that the mucous membrane of the bladder was congested, and the openings of the bladder were clear bilaterally with the spraying of urine and clear color, and we saw a new organism in the right side of the bladder behind the opening of the ureter, which was about 1.0 cm × 0.8 cm in size and was tipped, and we gave the power of electrocutaneous excision of 90 W and electrocoagulation of 100 W to electrically resect the bladder tumor and its surrounding mucosa in the range of 1 cm, deep to the muscle layer, complete hemostasis, removal of the tumor, F20 three-lumen catheter retained catheterization, injection of 20 mL of water, the operation went smoothly, the postoperative anamnesis, the specimen was sent for pathological examination.

Measure index

Self-rating Anxiety Scale: The Self-rating Anxiety Scale (SAS) is a self-reported measure of anxiety used primarily in adults. The scale consists of 20 items. Each item was scored out of a total of four points, ranging from one to four. This is then multiplied by 1.25 to obtain a standardized score. The SAS contains 20 items reflecting subjective feelings of anxiety, and each item is rated on a four-point scale according to the frequency of symptom occurrence, with 15 positive and five negative ratings. 1 means "none or very little of the time"; 2 means "a small percentage of the time"; 3 means "quite a lot of the time"; 4 means "present the vast majority or all of the time".

Self-Rating Depression Scale: The Self-Rating Depression Scale (SDS) is a self-report measure of the severity of depressive symptoms in adults developed by Zung in 1965 and consists of 20 items rated on a four-point Likert scale ranging from 1 to 4 (*i.e.*, none to all). The total score on the SDS index is obtained by summing the scores for each of the 20 items to obtain a total score, which is then normalized to a score by multiplying by 1.25. The SDS measures the severity of depressive symptoms in adults. With reference to the results of the national norm, the final criterion for the SDS was a total score of ≥ 53 for depressive symptoms and < 53 for no depressive symptoms[11].

Statistical analysis

A database was set up, and the data were entered using Epidata after double-checking. Data were entered after double-checking. SPSS software (version 26.0) was used to analyze the data. Count data were analyzed using the χ^2 test. Measurement data were expressed as mean \pm SD. The two groups before and after the intervention were compared using repeated-measures ANOVA, the two groups were compared using the two independent samples *t*-test, and the two groups within the groups were compared using the least significant difference procedure. Statistical significance was set at $P < 0.05$.

RESULTS

General information on the study population

A total of 120 participants were included in this study and categorized into the passive psychological state group ($n = 55$) and regular group ($n = 75$) based on depression and anxiety scores. Although the two groups of patients did not show significant differences in indicators such as sex, age, and work status, they showed statistical differences in indicators such as whether it was the first operation, economic status, education level, and marital status ($P < 0.05$). No significant difference was found in the baseline data between the study groups, proving their comparability (Table 1).

Logistic regression analysis affecting the occurrence of anxiety and depression in bladder cancer patients

Table 2 shows the distribution of variables with significant differences between the mental status disorder and conventional groups. Tables 3 and 4 show the logistic regression analyses affecting the occurrences of depression and anxiety in patients with bladder cancer, respectively. The results show that whether it is the first surgery, monthly income between 3000 and 6000, secondary or junior high school education level, and single, divorced, and widowed status are risk factors for these conditions.

Table 1 General information on the study population

		Passive group	Regular group	χ^2/t	P value
Gender (n)	Male	45	60	2.671	0.775
	Female	10	15		
Age (yr)		56.18 \pm 2.50	55.50 \pm 0.55		
Place of residence	Urban	20	25	1.824	0.556
	Countryside	35	50		
First surgery	Yes	11	41	14.743	0.001
	No	44	34		
Economic status (yuan/month)	< 3000	20	15	21.834	< 0.001
	3000-6000	29	42		
	> 6000	6	18		
Education	Below junior high school	12	19	14.823	< 0.001
	High school/secondary school	33	26		
	University/college and above	10	30		
Occupational status	Active	23	35	2.781	0.056
	Retired	21	33		
	Unemployed	4	7		
Marital status	Married	6	56	8.958	< 0.001
	Unmarried	11	7		
	Divorced/widowed	38	12		

Table 2 Table of assignments

Variable	Assignment
Whether first surgery	No = 0; yes = 1
Economic status	> 6000 = 0; 3000 = 1; 3000-6000 = 2
Education level	University/college and above = 0, high school/secondary school = 1, below junior high school = 2
Marital status	Married = 0; unmarried = 1; divorced/widowed = 2

Table 3 Logistic regression analysis affecting the occurrence of depression

Variable	OR	95%CI	Wald χ^2	P value
First surgery 1 vs 0	9.21	3.7-18.3	19.13	< 0.001
Economic status 1 vs 0	4.5	3.1-10.8	14.7	< 0.001
Economic status 2 vs 0	7.3	3.1-19.2	20.3	< 0.001
Education level 1 vs 0	5.1	2.4-13.3	19.2	< 0.001
Education level 2 vs 0	0.34	0.22-2.31	1.0	0.033
Married 1 vs 0	1.21	1.02-0.55	23.5	< 0.001
Married 2 vs 0	2.61	1.9-21.0	15.1	< 0.001

OR: Odds ratio; CI: Confidence interval.

DISCUSSION

With the development of society and the increase in environmental pollution, the number of cancer patients has shown an increasing trend every year. With the change in the medical model, the clinical treatment for cancer patients is not limited to symptomatic treatment but also focuses on the psychological health of cancer patients. In this study, we took bladder cancer patients as the main research object and analyzed the current situation and factors affecting the occurrence of depression and anxiety after PES in patients with non-muscle invasive bladder cancer. The results of the study found that among the 130 patients with bladder cancer, 55 (45.83%) had a negative psychological status. Logistic regression analysis showed that the first surgery, economic status, education level, and marital status were risk factors affecting the development of anxiety and depression in patients with bladder cancer.

Effect of number of operations on the psychological status of bladder cancer patients

Bladder cancer has a very high recurrence rate, and the recurrence rate of early-stage bladder cancer patients is 10%-30%. Some bladder cancer patients need to undergo a second surgery after PES[12]. Previous studies have found that most patients have significantly greater expectations for the first surgery than for the second and that multiple surgical treatments have made patients more anxious[13]. In the present study, non-first surgery was not only a factor influencing patients' anxiety but also a factor influencing patients' depression[14]. In addition, the adverse effects of electrosurgery are a factor in anxiety and depression. In recent years, most studies have found that post-electrosurgery patients often have urethral inflammation, urinary frequency, urgency, urinary pain, and other complications that greatly affect their quality of life[15]. Patients who underwent multiple surgeries had higher surgical risks and adverse reactions. Repeated post-operative reactions are also a type of torture for patients, affecting their sleep and work, and they are more prone to depression and anxiety than patients who have undergone their first surgery[16].

Effect of educational level on the psychological state of bladder cancer patients

For patients with cancer, the costs of surgery and chemotherapy are high. Patients with bladder cancer often require more than one year of chemotherapy after surgery, and the huge financial burden makes some patients face great economic pressure in addition to the pressure caused by the disease[17]. Therefore, financial pressure is more serious for patients with low monthly incomes. Previous studies found that some patients discontinued treatment mainly because of financial pressure[18]. In this study, we found that financial stress caused anxiety and depression in patients with bladder cancer. Therefore, when treating patients with financial difficulties, special attention should be paid to their psychological health, and the government should provide certain subsidies to cancer patients to help them treat the disease.

Effect of educational level on the psychological state of bladder cancer patients

Educational level affects how a person thinks about difficult events. Most studies have shown a significant correlation between the level of education and the state of depression[19]. It has been found that people with low levels of education are prone to depression, and those with high levels of education are generally more financially and socially resourceful and more concerned about their own health or physical condition and it can be concluded that between those with different levels of education. Differences in depression can start early in life, and those with low levels of education are more likely to have grown up in a poor environment with poor home occupations, diet, exercise habits, and access to healthcare, which are factors that can exacerbate their risk of depression as they grow older[20].

Effect of marital status on the psychological state of bladder cancer patients

The present study showed that the marital status of patients was also a major factor influencing depression and anxiety. This may be related to the atmosphere of home care for cancer patients during and after surgery[21]. Bladder cancer is a urological tumor; therefore, spouses are more important in patient care than in other kinship relationships[22]. When cancer is diagnosed, both the patient and the family are under a great deal of stress. Throughout the process, from diagnosis to treatment, the spouse usually takes on most of the emotional, financial, or functional support needed by the patient and plays a very important role in the prognosis and quality of life of cancer patients. In fact, married patients with cancer have higher survival rates than nonmarried patients.

Suggested strategies

To address the mental health problems of patients with non-muscle invasive bladder cancer, we propose the following strategies: First, strengthening preoperative psychological intervention; providing patients with assessment, counseling, and guidance on coping strategies through professional mental health teams; and helping them establish a positive mindset and coping mechanisms. Second, to enhance the knowledge of patients and their families about bladder cancer and its treatment, knowledge about bladder cancer should be popularized through health education and lectures so that patients can better understand the condition and reduce unnecessary fear and anxiety. Meanwhile, a sound postoperative psychological rehabilitation system should be established. Personalized rehabilitation plans, including cognitive-behavioral therapy, group counseling, and relaxation training, should be designed according to the specific conditions of the patients to alleviate their psychological pressure and improve their quality of life. We must also pay attention to patients' economic situations by enhancing the medical insurance system and setting up special funds to reduce their financial burden so that they can focus more on treatment and rehabilitation. Finally, we need to strengthen the training and education of healthcare professionals to enhance their understanding of and ability to deal with the mental health problems of patients with cancer. This step will ensure that patients can receive timely and effective psychological support. Through the integrated implementation of these strategies, we expect to improve the mental health status of

Table 4 Logistic regression analysis affecting the occurrence of anxiety

Variable	OR	95%CI	Wald χ^2	P value
First surgery 1 vs 0	12.88	4.4-30.7	20.92	< 0.001
Economic status 1 vs 0	0.75	0.31-10.8	14.7	< 0.001
Economic status 2 vs 0	3.21	2.5-21.6	20.3	< 0.001
Education level 1 vs 0	3.30	2.88-15.2	13.9	< 0.001
Education level 2 vs 0	1.29	1.11-9.03	3.9	0.08
Married 1 vs 0	6.72	3.21-29.9	3.90	0.12
Married 2 vs 0	2.14	1.92-34.0	15.1	< 0.001

OR: Odds ratio; CI: Confidence interval.

patients with non-muscle-invasive bladder cancer and promote their full recovery.

Strengths and limitations of this study

In this study, the occurrence of depression and anxiety in patients with bladder cancer was statistically analyzed, mainly using retrospective studies, and the history of patient pairs was complete, which provided a better description of the current status and influencing factors. However, unlike cohort studies, retrospective studies lack direct causal links. In addition, our study did not include a large sample of people to explore due to the stringent screening criteria for the study population. In the future, larger samples should be explored to ensure the robustness of the results.

CONCLUSION

This retrospective study analyzed morbidity-influencing factors affecting anxiety and depression in patients with bladder cancer after PES. In the future clinical treatment of patients with bladder cancer, attention should also be paid to their mental health, and recommendations and evidence should be provided for a good clinical prognosis.

FOOTNOTES

Author contributions: Lu B and Yan CY contributed equally to this work. Lu B, Ding M, Xu HB, and Yan CY designed the research study and Yan CY performed the research; Lu B and Yan CY analyzed the data and wrote the manuscript; and all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Suzhou Dushu Lake Hospital, No. 2023231011.

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

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

Data sharing statement: No other data available.

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S-Editor: Wang JJ

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P-Editor: Che XX

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Retrospective Study

Analysis of status and influencing factors of mental health in patients with systemic lupus erythematosus

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade A

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Alkhamees A, Saudi Arabia

Received: February 26, 2024

Revised: April 23, 2024

Accepted: May 6, 2024

Published online: June 19, 2024

Processing time: 114 Days and 11.5 Hours



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Abstract

BACKGROUND

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disorder with varied clinical courses and prognoses, not only did the patients suffer from physical impairment, but also various physical and psychiatric comorbidities. Growing evidence have suggested that mental disorders in SLE patients, can lead to various adverse consequences.

AIM

To explored the features and influencing factors of mental health in patients with SLE and clarifying the correlations between mental health and personality characteristics and perceived social support. The results would provide a basis for psychological intervention in patients with SLE.

METHODS

The clinical data of 168 patients with SLE admitted at the First Affiliated Hospital of Hainan Medical University between June 2020 and June 2022 were collected. Psychological assessment and correlation analysis were conducted using the Symptom Checklist-90 (SCL-90) and Perceived Social Support Scale, and the

collected data were compared with the national norms in China. The relevant factors influencing mental health were identified by statistical analysis. A general information questionnaire, the Revised Life Orientation Test, and Short-Form 36-Item Health Survey were employed to assess optimism level and quality of life (QoL), respectively.

RESULTS

Patients with SLE obtained higher scores for the somatization, depression, anxiety, and phobic anxiety subscales than national norms ($P < 0.05$). A correlation was identified between total social support and total SCL-90 score or each subscale ($P < 0.05$). The factors significantly affecting patients' mental health were hormone dosage and disease activity index (DAI) ($P < 0.05$). The average optimism score of patients with SLE was 14.36 ± 4.42 , and 30 cases were in the middle and lower levels. A positive correlation was found between optimism level and QoL scores.

CONCLUSION

Patients with SLE develop psychological disorders at varying degrees, which are significantly influenced by hormone dosage and DAI. Patients' mental health should be closely monitored during clinical diagnosis and treatment and provided adequate support in establishing positive, healthy thinking and behavior patterns and improving their optimism level and QoL.

Key Words: Systemic lupus erythematosus; Mental health; Quality of life; Influencing factors

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Core Tip: Patients with systemic lupus erythematosus suffer from various physical and psychiatric comorbidities. These serious forms of the disease can significantly impair activities of daily living and social roles. The identification of the factors that trigger these complications enables the causes to be determined and measures to be implemented to improve patient health.

Citation: Zhang X, Wang Z, Lin GL, Wei FZ, Zhuang YP, Xu WL, Zhang Q, Wu HT, He ZM, Yin XY, Liu Y, Mi L, Gong AM. Analysis of status and influencing factors of mental health in patients with systemic lupus erythematosus. *World J Psychiatry* 2024; 14(6): 829-837

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/829.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.829>

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disorder with varied clinical courses and prognoses [1]. The signs and symptoms can be inconspicuous or apparent, and the disease can affect one or multiple organ systems [2,3]. The high heterogeneity of clinical presentation and autoantibody profiles in SLE pose challenges in clinical decision making. The onset and progression of SLE is generally attributed to genetic factors, environmental exposure, and gene-environment interactions that trigger the collapse of adaptive and innate immunity [4,5]. While SLE is highly prevalent in young women, it can affect patients of any sex or age [6]. SLE can cause arthritis, serositis, nephritis, rash, scar, pigmentation, skin depression, hair loss, and neuropsychiatric problems, seriously impacting patients' quality of life (QoL) [7-10].

However, in addition to physical impairment, patients with SLE often suffer from various physical and psychiatric comorbidities [11,12]. Patients are at increased risk for mental disorders, including depression and anxiety, due to prolonged illness or long-term use of glucocorticoids (GCs) [13]. The prevalence of depression and anxiety in patients with SLE range from 2.1%-78.6% and 2.9%-84.9%, respectively [14]. More serious cases are accompanied by hallucinations, delusions, suicidal ideation, and other mental disorders and behavioral abnormalities. Studies have linked interactions among depression, anxiety, and SLE to an increased risk of suicidal ideation, low compliance to treatment, and dysfunction [15,16]. Growing evidence indicates that mental disorders, especially depression, in patients with SLE can cause multiple adverse outcomes, such as fatigue, neurocognitive difficulties, functional disability, subclinical atherosclerosis, and reduced health-related QoL. In fact, serious forms of the disease can be highly detrimental to activities of daily living and social roles. In a cross-sectional analysis of 80 patients with SLE conducted by Nowicka-Sauer *et al* [17], anxiety and depression together explained 43% of the differences in disease perception. Therefore, identifying the factors that trigger these complications helps determine the causes and allows the reasonable adjustment of these factors to improve patient health.

Despite the large number of patients with SLE in China, understanding of their mental health is limited. Therefore, we investigated and analyzed the psychological status, perceived social support, and dispositional optimism of patients with SLE to improve understanding of their mental health status and the influencing factors. The data would provide evidence for the development of treatment and intervention.

MATERIALS AND METHODS

Study subjects

The clinical data of 168 patients with SLE treated in the First Affiliated Hospital of Hainan Medical University, were collected. The eligibility criteria were as follows: (1) Met the criteria for the revised American College of Rheumatology for SLE; (2) age ≥ 18 years; (3) ability to read, understand, and complete forms; (4) voluntary enrollment; and (5) complete clinical data. The exclusion criteria were as follows: (1) Age < 18 years; (2) severe heart, brain, lung, kidney, and hematopoietic system damage; (3) hypertension, heart disease, diabetes, and other chronic diseases; and (4) mental illness and cognitive impairment.

Investigation methods

The clinical data collected from patients included age, sex, education level, and course of disease. Questionnaires and individual interviews were used to investigate the following items: (1) An assessment of patients' mental health status relative to national norms was performed using the Symptom Checklist-90 (SCL-90), a scale covering 90 symptoms categorized into 9 subscales (*i.e.*, somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism). The scale adopts a 5-point scoring system, with 0, 1, 2, 3, and 4 points indicating a little bit, moderately, quite a bit, and extremely, respectively; (2) perceived social support: the adequacy of perceived social support was assessed using the Perceived Social Support Scale (PSSS); Cronbach's α coefficient: 0.90, which consists of 12 items that assesses two sources of support (friend and family) and scored on a 5-point Likert scale. The possible total score ranges from 12 to 84 and is classified as low (12-36), intermediate, (37-60), or high (61-84); (3) optimism level: Optimism level was assessed using the Chinese version of the Revised Life Orientation Test (Cronbach's α coefficient: 0.72). The test consisted of 10 items, with 3 measuring optimism, 3 measuring pessimism, and 4 as fillers that are not scored. The other items are scored using a 5-point Likert scale, with the options ranging from "I strongly disagree (0 points)" to "I strongly agree (4 points)" and a maximum total score of 24 points. The score is positively associated with the optimism level. A total score of ≤ 13 , 14-18, or 19-24 indicates a low, moderate, or high dispositional level of optimism, respectively; and (4) short-Form 36-Item Health Survey (SF-36): We used the SF-36 (Cronbach's α coefficient: 0.80) to assess patients' health status. The scale includes 36 items on 8 dimensions, including physical functioning (PF)/social functioning, physical/emotional role, bodily pain (BP), general/mental health, and vitality (VT). Each dimension has a score range of 0-100, with higher scores indicating better functional status and QoL for that dimension.

Data gathering

Two nurses who participated in this study were selected as investigators and underwent unified training from the researchers. Questionnaires were distributed to patients by the researchers and investigators. The purpose and significance of the study, content of the survey, and method of completing the questionnaire were explained in detail to the patients with unified guidance. The questionnaire was distributed after obtaining the consent. During the questionnaire survey, any questions were answered on the spot, but no suggestions or hints were given. The questionnaire was anonymous and was returned on the spot after completion. In total, 168 of 180 questionnaires distributed were retrieved, with an effective recovery rate of 93.3%.

Statistical analyses

After reviewing all the data, statistical analyses and data entry were performed using SPSS 25.0. Continuous variables conforming to a normal distribution were expressed as mean \pm SD, and the *t*-test was used for statistical analysis. If nonnormally distributed, the data were expressed as median and interquartile range and compared using the rank-sum test. Categorical variables were expressed as number and percentage and analyzed using the chi-square test. Pearson correlation analysis was performed. $P < 0.05$ was considered statistically significant.

RESULTS

General information

In total, 168 of 180 (93.3%) questionnaires distributed were retrieved. Of the 168 participants, 38 were male and 130 were female, aged 18-63 years (mean \pm SD: 36.33 \pm 10.23 years), and had a disease course ranging from 2 months to 8 years (mean \pm SD: 3.57 \pm 2.43 years) (Table 1).

SCL-90 evaluation results

Compared with the national norms, the SCL-90 scores of the 168 patients with SLE were higher in the somatization, depression, anxiety, and phobic anxiety subscales (Table 2).

Correlation of SCL-90 score with disease course, hormone dosage, and disease activity index

Factors with significant differences in Table 2 were selected to analyze their correlation with disease duration, hormone dosage, and disease activity index (DAI). Hormone dosage was strongly correlated with the total, somatization, depression, and anxiety scores ($P < 0.05$). A significant association was also found between DAI and individual scores of all factors ($P < 0.05$) but not between disease course and SCL-90 score ($P > 0.05$; Table 3).

Table 1 Demographic data of 168 patients with systemic lupus erythematosus, *n* (%)

Demographic characteristics	Number of cases (<i>n</i> = 168)
Age	
18-30	52 (31.0)
31-40	65 (38.7)
41-50	37 (22.0)
> 50	14 (8.3)
Sex	
Male	38 (22.6)
Female	130 (77.4)
Course of disease	
≥ 1 yr	118 (70.2)
< 1 yr	50 (29.8)
Degree of education	
< High school	69 (41.1)
≥ High school	99 (58.9)
Marital status	
Single	46 (27.4)
Married	99 (58.9)
Divorced	23 (13.7)
Hormone dosage	
0	26 (15.5)
< 7.5	92 (54.8)
7.5-30	47 (28.0)
> 30	3 (1.7)
Disease activity index	
0-4	69 (41.1)
5-9	54 (32.1)
10-14	29 (17.3)
≥ 15	16 (9.5)

Correlation between total social support and SCL-90 scores

Among the 168 patients with SLE assessed by PSSS, the scores for total social support, family support, and friend support were 60.65 ± 7.61 , 24.61 ± 2.03 , and 36.04 ± 7.39 points, respectively. The total social support and friend support scores were negatively correlated with the total and subscale SCL-90 scores ($P < 0.05$). The family support score was significantly correlated with obsession-compulsion, interpersonal sensitivity, depression, and psychoticism subscale scores ($P < 0.05$; Table 4).

Optimism level and QoL scores

The total optimism score of the 168 patients with SLE was (14.36 ± 4.42), with low, medium, and high levels of optimism found in 30 (17.8%), 26 (15.5%), and 112 (66.7%) patients, respectively. The 168 patients obtained lower SF-36 scores in all dimensions than the national norms (Table 5).

Correlation between optimism level with QoL

The optimism level of patients with SLE was positively correlated with physical functioning, general health, VT, social functioning, and mental health scores on the SF-36 scale ($P < 0.05$; Table 6).

Table 2 Comparison of Symptom Checklist 90 scores of 168 patients with national norms

Categories	SLE (n = 168)	National norms in 2006 (n = 1890)	t	P value
Somatization	1.55 ± 0.63	1.42 ± 0.44	3.523	0.0004
Obsessive-compulsive	1.68 ± 0.52	1.66 ± 0.52	0.478	0.633
Interpersonal sensitivity	1.53 ± 0.44	1.51 ± 0.49	0.511	0.609
Depression	1.58 ± 0.54	1.49 ± 0.47	2.348	0.019
Anxiety	1.53 ± 0.55	1.34 ± 0.38	5.952	< 0.0001
Hostility	1.50 ± 0.87	1.49 ± 0.51	0.227	0.821
Phobic anxiety	1.35 ± 0.44	1.27 ± 0.39	2.52	0.012
Paranoid ideation	1.50 ± 0.44	1.44 ± 0.47	1.594	0.111
Psychoticism	1.36 ± 0.46	1.33 ± 0.39	0.941	0.347
Total	135.66 ± 36.03	130.02 ± 33.63	2.071	0.038

SLE: Systemic lupus erythematosus.

Table 3 Correlation of Symptom Checklist 90 score with course of disease, hormone dosage, and disease activity index in 168 patients with systemic lupus erythematosus

	Course of disease		Hormone dosage		Disease activity index	
	r	P value	r	P value	r	P value
Somatization	0.025	0.744	0.199	0.009	0.423	< 0.0001
Depression	-.006	0.931	0.391	< 0.0001	0.226	0.003
Anxiety	0.039	0.613	0.293	0.0001	0.246	0.001
Phobic anxiety	0.144	0.062	0.013	0.8664	0.205	0.008
Total	0.082	0.289	0.210	0.006	0.268	0.0004

DISCUSSION

So far, SLE has not been fully clarified etiologically. Due to disease recurrence, unsatisfactory therapeutic effect, high financial burden, and other unfavorable factors, patients with SLE develop significant negative emotions during treatment that seriously affect their physical and mental health[18]. Despite progress in diagnosis and treatment, patients with SLE have a high prevalence of mental health disorders that profoundly impact QoL, leading to an increase in disability and premature death[19]. Hence, monitoring their mental health and analyzing the influencing factors is crucial.

In this study, SCL-90 was used to evaluate the psychological status of 168 patients with SLE relative to the 2006 national norms in China. The results showed significantly higher somatization, depression, and anxiety scores in patients with SLE *vs* the national norms, indicating worse mental health in patients with SLE than the general population. Hormone dosage and DAI were identified as important influencing factors. SLE is a chronic disorder with a long disease course and recurrence. Drug treatment can induce multiorgan side effects, and hormone use may cause facial changes, which in turn predispose patients to psychological problems, such as anxiety, fear, loneliness, and depression[20]. In some studies, DAI, especially diseases of the cutaneous mucous membrane and musculoskeletal areas, has been associated with increased symptoms of depression and anxiety[21,22]. However, higher disease activity in SLE has not been associated with depression and anxiety[23-25]. However, our study found that the level of disease activity was significantly related to psychological scores, such as those for depression and anxiety. We believe that the higher the disease activity, the more serious the dysfunction in various systems and organs of the body and the worse the psychological status and QoL. Nery *et al*[26] reported that disease activity in SLE as determined using the SLEDAI was related to depression severity. In addition, GCs, both immunosuppressants and biologics, have always been the cornerstone of SLE treatment[27]. However, long-term use of GCs may cause irreversible organ impairment, leading to QoL decline and even increased mortality. For instance, the risk increases significantly when the prednisone maintenance dose is more than 7.5 mg/day; however, lower doses have also been demonstrated to be potentially harmful[28-30]. Therefore, the hormone dosage also affects patients' physical and mental health.

We also evaluated patients' optimism level and QoL. The average optimism level score of the 168 patients with SLE was 14.36 ± 4.42 . Among them, 30 (17.8%) had a low optimism level, 112 (66.7%) had a medium optimism level, and 26 (15.5%) had a high optimism level. Optimism is an important component of psychological reserve ability and plays a vital

Table 4 Correlation analysis between Symptom Checklist 90 score and social support in 168 patients with systemic lupus erythematosus

	PSSS		Family support		Friend support	
Total score	60.65 ± 7.61		24.61 ± 2.03		36.04 ± 7.39	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
Somatization	-0.408	< 0.0001	-0.098	0.205	-0.394	< 0.0001
Obsessive-compulsive	-0.358	< 0.0001	-0.201	0.009	-0.313	< 0.0001
Interpersonal sensitivity	-0.292	0.0001	-0.211	0.006	-0.242	0.002
Depression	-0.367	< 0.0001	-0.154	0.046	-0.336	< 0.0001
Anxiety	-0.300	< 0.0001	-0.074	0.340	-0.289	0.0001
Hostility	-0.466	< 0.0001	-0.1011	0.1920	-0.452	< 0.0001
Phobic anxiety	-0.305	< 0.0001	-0.081	0.298	-0.292	0.0001
Paranoid ideation	-0.285	0.0002	-0.068	0.383	-0.275	0.0003
Psychoticism	-0.267	0.0005	-0.165	0.032	-0.229	0.0028
Total score	-0.298	< 0.0001	-0.077	0.318	-0.285	0.0002

PSSS: Perceived Social Support Scale.

Table 5 Optimism level and quality of life scores of 168 patients with systemic lupus erythematosus

Score	Number of cases (<i>n</i> = 168)	National norms (<i>n</i> = 17754)	<i>t</i>	<i>P</i> value
Optimism level	14.36 ± 4.42	-	-	-
Physical functioning	60.99 ± 3.05	89.9 ± 16.9	22.169	< 0.0001
Role-physical	60.85 ± 3.41	77.5 ± 34.8	6.201	< 0.0001
Bodily pain	58.62 ± 3.46	82.2 ± 16.9	18.081	< 0.0001
General health	59.07 ± 4.58	62.5 ± 17.8	2.497	0.013
Vitality	56.46 ± 2.92	68.2 ± 17.6	8.645	< 0.0001
Social functioning	65.62 ± 3.46	81.6 ± 19.9	10.407	< 0.0001
Role-emotional	53.32 ± 1.40	67.8 ± 39.4	4.763	< 0.0001
Mental health	52.54 ± 2.79	68.5 ± 16.9	12.238	< 0.0001

role in regulating patients’ physiological function and psychological state. A sense of optimism helps patients cope with the heavy burden associated with chronic diseases, thereby alleviating the physical and mental pain caused by disease [31]. On the contrary, pessimistic and negative coping strategies may affect patients’ medication compliance. A low optimism level can worsen the patient’s fragile psychology, resulting in ineffective responses to the problems associated with or caused by the disease, inducing anxiety and depression, aggravating the disease burden, and even inducing suicidal thoughts in serious cases[32]. The scores for all dimensions of the QoL scale were lower than those of the national norms, indicating that patients with SLE have a lower QoL. Subsequently, optimism level was positively correlated with QoL, similar to the findings of Kepka *et al*[33]. Those with lower optimism levels are more likely to use abnormal and inappropriate coping strategies when faced with stressful events, resulting in lower QoL scores. However, optimism level had little effect on PF and BP, possibly because the SF-36 components are mostly objective and less affected by individual patients’ psychological resilience, optimism, and response pattern to threats. Therefore, encouraging patients to maintain an optimistic and balanced state of mind is conducive to their development of a corresponding psychological reserve, thereby alleviating anxiety and depression symptoms and enabling patients to calmly face the burden brought by diseases and improve their QoL.

However, this study has some limitations. The results obtained in this study only provide a theoretical explanation of the psychological state of patients with SLE. Intervention measures should be implemented according to the severity of the psychological disorder. Thus, further longitudinal studies and interventional trials are warranted to validate the current findings and confirm the efficacy of tailored psychological interventions in improving mental health outcomes among patients with SLE.

Table 6 Correlation of optimism level with quality of life in 168 patients with systemic lupus erythematosus

	Optimism level	
	<i>r</i>	<i>P</i> value
Physical functioning	0.172	0.026
Role-physical	0.018	0.814
Bodily pain	0.055	0.479
General health	0.474	< 0.0001
Vitality	0.280	0.0002
Social functioning	0.338	< 0.0001
Role-emotional	0.111	0.152
Mental health	0.347	< 0.0001

CONCLUSION

In conclusion, patients with SLE develop psychological disorders, among which somatization, depression, anxiety, and phobic anxiety are the most significant. Hormone dosage and DAI are significant factors influencing mental health. In clinical practice, medical staff should be patient-centered, understand the disease burden of patients in all aspects, and consider the psychological distress of patients while monitoring disease activity and severity.

FOOTNOTES

Author contributions: Zhang X, Wang Z, Mi L and Gong AM designed the research; Zhang X, Wang Z, Lin GL, Wei FZ screened patients, acquired clinical data; Zhuang YP, Xu WL, Zhang Q, Wu HT, He ZM, Yin XY, Liu Y, Mi L and Gong AM collected questionnaires and performed individual interviews; Zhang X, Wang Z, Mi L and Gong AM conducted the analysis and provided guidance for the research; Zhang X, Wang Z, Mi L and Gong AM performed data analysis and prepared the first draft of the manuscript. Zhang X proposed, designed the research, performed data analysis and prepared the first draft of the manuscript. Wang Z was responsible for patient screening, enrollment, collection of clinical data. Both authors have made crucial and indispensable contributions towards the completion of the project and thus qualified as the co-first authors of the paper. All authors reviewed and approved the final manuscript. Zhang X and Wang Z contributed equally to this work and are co-first authors. Both Mi L and Gong AM have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. Mi L applied for and obtained the funds for this research project. Mi L conceptualized, designed, and supervised the whole process of the project. Mi L searched the literature, revised and submitted the early version of the manuscript. Gong AM was instrumental and responsible for data re-analysis and re-interpretation, comprehensive literature search, preparation and submission of the current version of the manuscript. This collaboration between Mi L and Gong AM is crucial for the publication of this manuscript and other manuscripts still in preparation.

Supported by National Natural Science Foundation of China, No. 81760840 and No. 82160874; and Natural Science Foundation of Hainan Province, No. 2019RC206.

Institutional review board statement: This study was approved by the Ethic Committee of Hainan Medical University (Approval No. HYLL-2023-455).

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

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

Data sharing statement: The data used in the above analysis are available upon reasonable request from the corresponding author.

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S-Editor: Qu XL

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Retrospective Study

Relationship between preoperative psychological stress and short-term prognosis in elderly patients with femoral neck fracture

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Ciobanu AM,
Romania

Received: February 28, 2024

Revised: April 23, 2024

Accepted: May 6, 2024

Published online: June 19, 2024

Processing time: 112 Days and 9.9
Hours



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Abstract

BACKGROUND

Older adults are at high risk of femoral neck fractures (FNFs). Elderly patients face and adapt to significant psychological burdens, resulting in different degrees of psychological stress response. Total hip replacement is the preferred treatment for FNF in elderly patients; however, some patients have poor postoperative prognoses, and the underlying mechanism is unknown. We speculated that the postoperative prognosis of elderly patients with FNF may be related to preoperative psychological stress.

AIM

To explore the relationship between preoperative psychological stress and the short-term prognosis of elderly patients with FNF.

METHODS

In this retrospective analysis, the baseline data, preoperative 90-item Symptom Checklist score, and Harris score within 6 months of surgery of 120 elderly patients with FNF who underwent total hip arthroplasty were collected. We analyzed the indicators of poor short-term postoperative prognosis and the ability of the indicators to predict poor prognosis and compared the correlation between the indicators and the Harris score.

RESULTS

Anxiety, depression, garden classification of FNF, cause of fracture, FNF reduction quality, and length of hospital stay were independent influencing factors for poor short-term postoperative prognoses in elderly patients with FNF ($P < 0.05$). The areas under the curve for anxiety, depression, and length of hospital

stay were 0.742, 0.854, and 0.749, respectively. The sensitivities of anxiety, depression, garden classification of FNF, and prediction of the cause of fracture were 0.857, 0.786, 0.821, and 0.821, respectively. The specificities of depression, FNF quality reduction, and length of hospital stay were the highest at 0.880, 0.783, and 0.761, respectively. Anxiety, depression, and somatization scores correlated moderately with Harris scores ($r = -0.523$, -0.625 , and -0.554 ; all $P < 0.001$).

CONCLUSION

Preoperative anxiety, depression, and somatization are correlated with poor short-term prognosis in elderly patients with FNF and warrant consideration.

Key Words: Psychological stress; Old age; Femoral neck fracture; Hip replacement; Short-term prognosis; Correlation

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Core Tip: Femoral neck fractures (FNF) are primarily caused by the loss of osteoporotic bone mass, and they tend to affect elderly adults. Some elderly patients with FNF have poor post-surgical outcomes due to unknown causes. We retrospectively analyzed the clinical data of 120 elderly patients with FNF and found that preoperative psychological stress was associated with a poor short-term prognosis in these patients, which is a breakthrough discovery in the understanding of the cause of poor prognosis among elderly patients with FNF.

Citation: Fu WH, Hu ZL, Liao YJ, Chen RJ, Qiu JB, Que WT, Wang WT, Li WH, Lan WB. Relationship between preoperative psychological stress and short-term prognosis in elderly patients with femoral neck fracture. *World J Psychiatry* 2024; 14(6): 838-847

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/838.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.838>

INTRODUCTION

A femoral neck fracture (FNF) occurs between the femoral head and base of the femoral neck caused by direct or indirect violent force. FNF accounts for approximately 3.6% and 54% of total and medullary fractures, respectively[1]. This fracture type is primarily associated with decreased bone mass due to osteoporosis[2]. Older people often have osteoporosis and are prone to developing FNF when exposed to external forces, such as falls and collisions[3]. Due to the peculiarity of the circulatory system of the femoral neck, an intracapsular hematoma is formed from local hemorrhage after FNF, resulting in increased pressure on the joint capsule. Simultaneously, the displacement of the fracture end distorts and compresses the blood vessels of the supporting band, leading to the collapse or ischemic necrosis of the femoral head[4].

Surgery, especially intraoperative internal fixation, can eliminate the tortuosity and compression of the local vessels at the site of FNF, restore blood supply, and correct anatomical position. Recently, with the continuous improvement in medical technology and optimization of orthopedic internal fixation materials in China, total hip replacement for FNF treatment has advanced and is one of the preferred options for patients with FNF. However, in clinical practice, some elderly patients still have an unsatisfactory postoperative prognosis. Statistically, the mortality rate of FNF among elderly patients within 1 year of surgery is as high as 14.2%-21.6%, and 50.5% of survivors have lifelong disabilities, which seriously affect their quality of life[5]. Currently, the specific cause of poor prognosis following FNF surgery is unknown.

Psychological stress refers to the adaptive nervous response to the imbalance in objective requirements and coping ability under the action of certain environmental stimuli, including emotional, self-psychological defense, and behavioral responses[6]. Studies have shown that patients with FNF experience different degrees of negative psychological states and stress reactions[7,8]. Patients with FNF often undergo treatment and rehabilitation with long duration and are often under much pressure. Limited mobility and loss of basic abilities can cause anxiety and depression. Elderly patients who do not know much about the disease and surgical procedures tend to worry too much, causing uneasiness, anxiety, depression, and other negative psychology[9]. Therefore, we speculated that preoperative psychological stress may be related to the prognosis of elderly patients with FNF. Currently, there are few reports on the correlation between psychological stress and the prognosis of FNF. Therefore, this study aimed to analyze the correlation between preoperative psychological stress state and the short-term prognosis of elderly patients with FNF to lay a foundation for improving their prognosis.

MATERIALS AND METHODS

Clinical data

This was a retrospective study. We enrolled 120 elderly patients with FNF who underwent total hip replacement at

Longyan First Affiliated Hospital of Fujian Medical University between May 2021 and May 2023. The selected patients were those: (1) With FNF confirmed using X-ray and computed tomography examination^[10]; (2) With unilateral fresh fracture; (3) That underwent total hip replacement; (4) Age > 18 years; (5) With normal hip function before FNF; (6) That received no intervention to improve psychological stress before and within 6 months of surgery; and (7) That provided consent to access and refer to their treatment data.

The excluded patients were those: (1) With fractures of other parts of the ipsilateral lower extremity; (2) With severe open injury or injury to critical blood vessels and nerves in the hip; (3) With damage to the head, chest, and other parts of the organ system; (4) With pathological or old fractures; (5) That died within 6 months of surgery; and (6) Whose general and follow-up data were incomplete.

Collected information

We collected general information, such as: (1) Sex, age, body mass index, comorbidities, fracture site, garden classification of FNF, cause of fracture, FNF reduction quality, surgical situation, length of hospital stay, intraoperative hypotension, postoperative sarcopenia, and postoperative complications; (2) Preoperative psychological stress state, including Symptom Checklist-90 (SCL-90) scores for anxiety (ANX), depression (DEP), hostility (HOS), interpersonal sensitivity (IS), obsessive-compulsive disorder (OCD), paranoia (PAR), phobia (PHOB), psychosis (PSY), and somatization (SOM); and (3) Follow-up data, including functional recovery of the hip joint assessed using the Harris hip scores within 6 months of surgery.

Evaluation criteria for psychological stress state

Psychological stress was assessed using the SCL-90 standard score^[11], which includes nine assessment items: ANX for the appearance of worry, anxiety, nervousness, fear, and restlessness; DEP for depression, loneliness, and sadness; HOS for the emergence of anger, hostility, and other emotions in patients; IS for interpersonal problems, such as trouble communicating and unwillingness to engage with others; OCD for presence of compulsive behaviors, such as ruminating, doing something, and checking; PAR for emergence of paranoid thoughts, such as distrust and suspicion; PHOB for the emergence of fear emotions, such as fear and dread of certain things or situations; PSY for the appearance of psychotic symptoms, such as delusions and hallucinations; and SOM for appearance of physical symptoms, such as discomfort, pain, and paresthesia.

The scale comprehensively evaluated the patients' recent actual feelings based on a five-level scoring system, with scores of 1, 2, 3, 4, and 5 indicating none, mild, moderate, partial, and severe, respectively. The higher the score, the more serious the psychological stress experienced by patients. Cronbach's α coefficient of SCL-90 was 0.85, indicating that the scale had good reliability and validity.

Surgical prognosis evaluation criteria

The hip joint function score (Harris score) within 6 months of surgery^[12] was used to evaluate patients' hip joint pain, function, deformity, and range of motion with a maximum score of 100. Scores > 90, 80-89, 70-79, and < 70 indicate excellent, good, fair, and poor functions, respectively. The scale has good reliability and validity, with a Cronbach's α is 0.89, which makes it suitable for the prognostic evaluation of FNF.

Other evaluation indicators

FNF reduction quality was assessed using immediate postoperative anterolateral radiographs. FNF reduction quality was divided into grades A, B, and C. Grade A is described by fracture point alignment deviation of < 15°, and femoral neck trunk angle of 125°-140°; grade B, fracture end of 15°-30° offset, and femoral neck trunk angle of 120° to < 140° or > 140°-150°; and grade C, fracture end alignment deviation of > 30° and femoral neck stem angle of < 125° or > 150°^[13].

Methods of total hip replacement

The surgeon administered general anesthesia *via* inhalation to the patients, and thereafter, the patients were placed in a healthy lateral position to cut their skin, subcutaneous tissue, and muscle within the anterolateral hip joint. After the joint capsule was opened, the femoral neck was fully exposed, the femoral neck stump was trimmed at the upper edge of the lesser trochanter (1.5 cm), and the femoral head was removed. The truncated surface of the femoral neck was kept perpendicular to the longitudinal axis of the femoral neck. The remnant tissue of the round ligament of the fossa ovale (known as the Harris fossa) was removed entirely, and the femoral bone marrow cavity was enlarged with a pulp file, which was ground along 45° extension and 15° anteriorization to the wall of the acetabulum to penetrate the blood vessels. The acetabular cup had an abduction angle of approximately 40° and a forward angle of approximately 15°. The diameter of the femoral head was measured, and an artificial femoral head was selected. Based on the bone density of the patient, biological (forward inclination of the femoral prosthesis was approximately 15°) or bone-cement prostheses were selected. The hip joint was reset using the prosthesis test model, and the prosthesis was installed accordingly. Active bleeding was detected and hemostasis was stopped. The operated site opening was rinsed with normal saline, a drainage tube was inserted, and closed with sutures. All patients underwent postoperative antibiotic intervention, and radiographic re-examination was conducted promptly. The drainage tube was removed 3 d after surgery, and rehabilitation training began 28 d after surgery.

Grouping

Those with Harris scores of ≥ 80 and < 80 were assigned to the good and poor prognosis groups, respectively.

Statistical treatment

We used SPSS 23.0 statistical software (IBM, Armonk, NY, United States) for data analysis. We represented measurement data with a normal distribution using the mean and standard deviation and compared the two groups using a *t*-test. Meanwhile, we presented measurements that did not conform to normal distribution using median (25th percentile, 75th percentile). Count data were expressed as cases and percentages using the χ^2 test or exact probability method. A logistic regression model was used to analyze factors influencing poor postoperative short-term prognosis in elderly patients with FNF. The receiver operating characteristic (ROC) curve and area under the curve (AUC) were used to analyze the predictive ability of the indicators for poor prognosis. Finally, we performed correlation analysis using Pearson or Spearman correlation coefficients in which $|r| > 0.8$ indicates a high correlation, $0.5 < |r| \leq 0.8$ moderate correlation, $0.3 < |r| \leq 0.5$ low correlation, and $|r| \leq 0.3$, no linear correlation between the variables. Statistical significance was established at $\alpha = 0.05$.

RESULTS

General data of patients in poor and good prognostic groups

Of the 120 elderly patients with FNF enrolled in this study, 92 and 28 (23.33%) had good and poor prognoses, respectively, within 6 months of surgery. The proportion of type IV garden classification of FNF, high-energy injury, and grade C FNF reduction quality in the poor prognosis group was higher, and the hospital stay was longer than those in the good prognosis group (all $P < 0.05$) (Table 1).

Preoperative SCL-90 scores in the poor and good prognosis groups

The ANX, DEP, and SOM scores in the poor prognosis group were higher than those in the good prognosis group (all $P < 0.05$) (Table 2).

Analysis of the influencing factors of poor short-term prognosis in elderly patients with FNF

Indicators that are significantly different between the poor and good prognosis groups (garden classification of FNF, cause of fracture, FNF reduction quality, length of hospital stay, ANX, DEP, and SOM) were taken as independent variables, and 6-month prognosis (good prognosis, 0; poor prognosis, 1) was input into the logistic regression model for analysis. We found that ANX, DEP, garden classification of FNF, cause of fracture, FNF reduction quality, and length of hospital stay were independent factors influencing poor postoperative short-term prognosis in elderly patients with FNF ($P < 0.05$) (Table 3).

Efficacy of indicators influencing poor short-term prognosis in elderly patients with FNF after surgery

ROC curve analysis showed that the AUCs of ANX, DEP, garden classification of FNF, cause of fracture, FNF reduction quality, and length of hospital stay were all above 0.6, and they were predictors of poor short-term prognosis in elderly patients with FNF. The AUCs for ANX, DEP, and length of hospital stay were 0.742, 0.854, and 0.749, respectively. The sensitivities of ANX, garden classification of FNF, cause of fracture, and DEP prediction were 0.857, 0.821, 0.821, and 0.786, respectively. The specificities of DEP, FNF reduction quality, and length of hospital stay were 0.880, 0.783, and 0.761, respectively (Table 4 and Figure 1).

Correlation between influencing indicators and Harris score

The mean 6-month postoperative Harris score was 83 (80-89). The ANX, DEP, and SOM scores were moderately correlated with the Harris scores ($r = -0.523, -0.625, \text{ and } -0.554$; all $P < 0.001$). There was a weak correlation between the three indicators (ANX, DEP, and SOM) (Table 5 and Figure 2).

DISCUSSION

Total hip replacement is widely believed to be an effective method for FNF treatment, as it is characterized by ease of operation, short operation time, prompt fracture healing, and a good Harris effect[14]. However, based on clinical experience, doctors know that the degree of FNF, postoperative FNF reduction quality, postoperative complications, and other factors can cause postoperative joint swelling, pain, and other uncomfortable symptoms in patients, which may affect postoperative prognosis. In this study, of the 120 elderly patients with FNF, 23.33% had a poor prognosis, similar to the results reported by Lang *et al*[15].

After statistical analysis, we observed type IV garden classification of FNF in the elderly patients with FNF caused by a high-energy injury with grade C FNF reduction quality, which was unfavorable for short-term prognosis. In addition, a prolonged hospital stay may indicate a poor short-term prognosis. Regarding the SCL-90 scale, which describes the psychological stress state of the patients, only ANX and DEP had a significant impact on the short-term prognosis of the patients. The AUCs and sensitivities of the two indicators were high (> 0.7) in predicting the short-term prognosis of elderly patients with FNF.

These results indicate that anxiety and depression have significant effects on the short-term prognosis of elderly patients with FNF undergoing total hip arthroplasty after adjusting for the garden classification of FNF, cause of fracture,

Table 1 General data of patients in the poor and good prognosis groups

Data	Poor prognosis group (n = 28)	Good prognosis group (n = 92)	χ^2/t	P value
Sex, n (%)			0.857	0.354
Male	6 (21.43)	28 (30.43)		
Female	22 (78.57)	64 (69.57)		
Age (mean \pm SD, yr)	65.72 \pm 4.39	66.35 \pm 4.26		
Body mass index (mean \pm SD, kg/m ²)	20.13 \pm 2.29	20.06 \pm 2.32		
Complications, n (%)				
Hypertension	6 (21.43)	20 (21.74)	0.001	0.972
Diabetes	5 (17.86)	18 (19.57)	0.040	0.841
Hyperlipidemia	3 (10.71)	15 (16.30)	0.179	0.672
Abnormal liver function	4 (14.29)	16 (17.39)	0.009	0.923
Fracture site, n (%)			0.186	0.666
left side	15 (53.57)	45 (48.91)		
right side	13 (46.43)	47 (51.09)		
Garden classification of FNF, n (%)			12.179	< 0.001
Type III	5 (17.86)	51 (55.43)		
Type IV	23 (82.14)	41 (44.57)		
Cause of fracture, n (%)			7.461	0.006
Low-energy damage	5 (17.86)	43 (46.74)		
High-energy damage	23 (82.14)	49 (53.26)		
FNF reduction quality, n (%)			10.645	0.005
Grade A	8 (28.57)	40 (43.48)		
Grade B	5 (17.86)	32 (34.78)		
Grade C	15 (53.57)	20 (21.74)		
Operational conditions				
Operation time (min)	108.62 \pm 14.39	107.71 \pm 15.02	0.283	0.777
Intraoperative blood loss (mL)	362.22 \pm 25.68	359.31 \pm 23.47	0.562	0.575
Intraoperative blood transfusion (mL)	283.36 \pm 52.47	278.55 \pm 55.36	0.407	0.685
Postoperative drainage volume (mL)	173.25 \pm 49.62	171.24 \pm 51.07	0.184	0.855
Length of hospital stay (d)	21.03 \pm 4.71	17.03 \pm 4.71	3.935	< 0.001
Intraoperative hypotension			0.076	0.783
Yes	13 (46.43)	40 (43.48)		
No	15 (53.57)	52 (56.52)		
Postoperative sarcopenia			0.758	0.384
Yes	10 (35.71)	25 (27.17)		
No	18 (64.29)	67 (72.83)		
Postoperative complications			0.149	0.699
Yes	6 (21.43)	23 (25.00)		
No	22 (78.57)	69 (75.00)		

FNF: Femoral neck fracture.

Table 2 Preoperative Symptom Checklist-90 scores of the poor and good prognosis groups

SCL-90	Poor prognosis group (n = 28)	Good prognosis group (n = 92)	t	P value
ANX	27.46 ± 3.35	24.17 ± 3.42	4.478	< 0.001
DEP	33.56 ± 2.34	30.25 ± 2.14	7.011	< 0.001
HOS	14.03 ± 2.51	14.72 ± 2.53	1.266	0.208
IS	16.12 ± 2.37	16.23 ± 2.25	0.224	0.823
OCD	17.36 ± 3.52	17.42 ± 3.37	0.082	0.935
PAR	16.13 ± 3.16	16.24 ± 2.88	0.173	0.863
PHOB	14.11 ± 2.58	14.06 ± 1.88	0.112	0.911
PSY	20.21 ± 3.46	20.17 ± 3.55	0.053	0.958
SOM	22.61 ± 3.18	19.23 ± 4.12	3.990	< 0.001

SCL-90: Symptom Checklist-90; ANX: Anxiety; DEP: Depression; HOS: Hostility; IS: Interpersonal sensitivity; OCD: Obsessive-compulsive disorder; PAR: Paranoid; PHOB: Phobia; PSY: Psychosis; SOM: Somatization.

Table 3 Correlation between indicators and prognosis of patients with Femoral neck fracture after surgery

Independent variables	B	SE	Wals	P value	OR (95%CI)
ANX	0.326	0.153	4.520	0.034	1.385 (1.026-1.870)
DEP	0.522	0.196	7.114	0.008	1.685 (1.148-2.472)
SOM	0.221	0.127	3.034	0.082	1.247 (0.973-1.599)
Garden classification of FNF	1.633	0.795	4.226	0.040	5.121 (1.079-24.303)
Cause of fracture	3.096	1.464	4.476	0.034	22.119 (1.256-389.623)
FNF reduction quality			6.931	0.031	
Level A	2.523	1.361	3.436	0.064	12.470 (0.865-179.753)
Level B	-1.686	0.974	2.993	0.084	0.185 (0.027-1.251)
Length of hospital stay	0.260	0.089	8.564	0.003	1.297 (1.090-1.544)

FNF: Femoral neck fracture; ANX: Anxiety; DEP: Depression; SOM: Somatization; B: Regression coefficient; SE: standard error; OR: Odds ratio; CI: Confidence interval.

Table 4 Receiver operating characteristic curve analysis

Variables	AUC	P value	95%CI	Sensitivity	Specificity	Optimum cutoff value
ANX	0.742	< 0.001	0.641-0.844	0.857	0.533	24.5
DEP	0.854	< 0.001	0.760-0.947	0.786	0.880	32.5
Garden classification of FNF	0.688	0.003	0.582-0.794	0.821	0.554	0.5
Cause of fracture	0.644	0.021	0.534-0.755	0.821	0.467	0.5
FNF reduction quality	0.648	0.018	0.524-0.772	0.536	0.783	2.5
Length of hospital stay	0.749	< 0.001	0.640-0.858	0.750	0.761	20.5

FNF: Femoral neck fracture; ANX: Anxiety; DEP: Depression; AUC: Area under the curve; CI: Confidence interval.

Table 5 Correlation between influence indicators and Harris score

Influence indicators		ANX	DEP	SOM	Garden classification of FNF	Cause of fracture	FNF reduction quality	Length of hospital stay
Harris scores	R	-0.523	-0.625	-0.554	-0.253	-0.250	-0.269	-0.222
	P value	< 0.001	< 0.001	< 0.001	0.005	0.006	0.003	0.015
ANX	R		0.455	0.489	0.084	0.141	0.205	0.092
	P value		< 0.001	< 0.001	0.363	0.124	0.025	0.316
DEP	R			0.495	0.207	0.169	0.219	0.148
	P value			< 0.001	0.023	0.065	0.016	0.107
SOM	R				0.158	0.080	0.202	0.227
	P value				0.084	0.384	0.027	0.013
Garden classification of FNF	R					0.225	0.199	0.073
	P value					0.013	0.029	0.428
Cause of fracture	R						0.621	0.161
	P value						< 0.001	0.079
FNF reduction quality	R							0.197
	P value							0.031

FNF: Femoral neck fracture; ANX: Anxiety; DEP: Depression; SOM: Somatization; R: correlation coefficient.

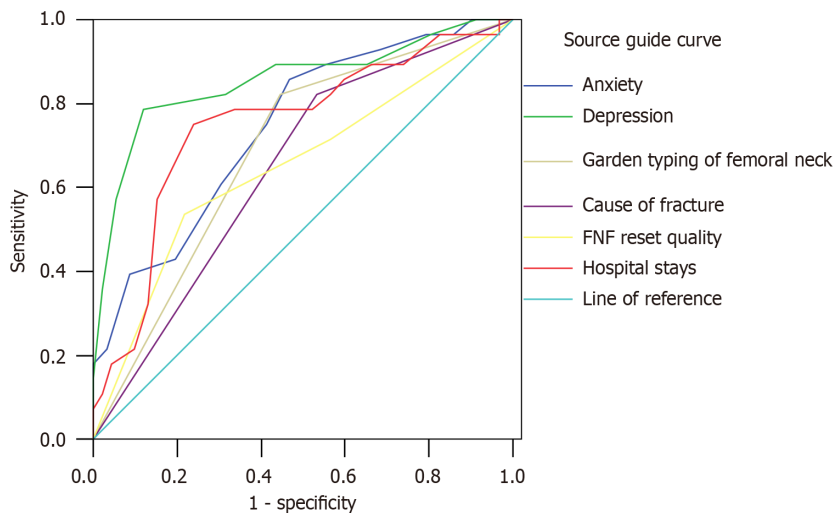


Figure 1 Receiver operating characteristic curve of influence indicators predicting poor short-term prognosis in elderly femoral neck fracture patients. FNF: Femoral neck fracture.

FNF reduction quality, length of hospital stay, and other influencing variables, whereas somatization has no effect on the prognosis. After a fracture, the qi mechanism (the normal operation mechanism of qi in the human body) in patients with FNF cannot rise and fall owing to sudden trauma and stress response, resulting in the blockage of qi and blood, which makes the patients prone to psychological disorders and aggravated condition[7]. Total hip replacement quickly restores limb function and minimizes complications in elderly patients with FNF. However, owing to the decrease in patients' organ functional reserve and the influence of complications, such as pain, delirium, and thrombosis, some patients underwent prolonged bed rest after surgery, making it difficult for them to participate in effective active and passive training and making them worry about their prognosis, leading to anxiety, depression, and other negative emotions, thus

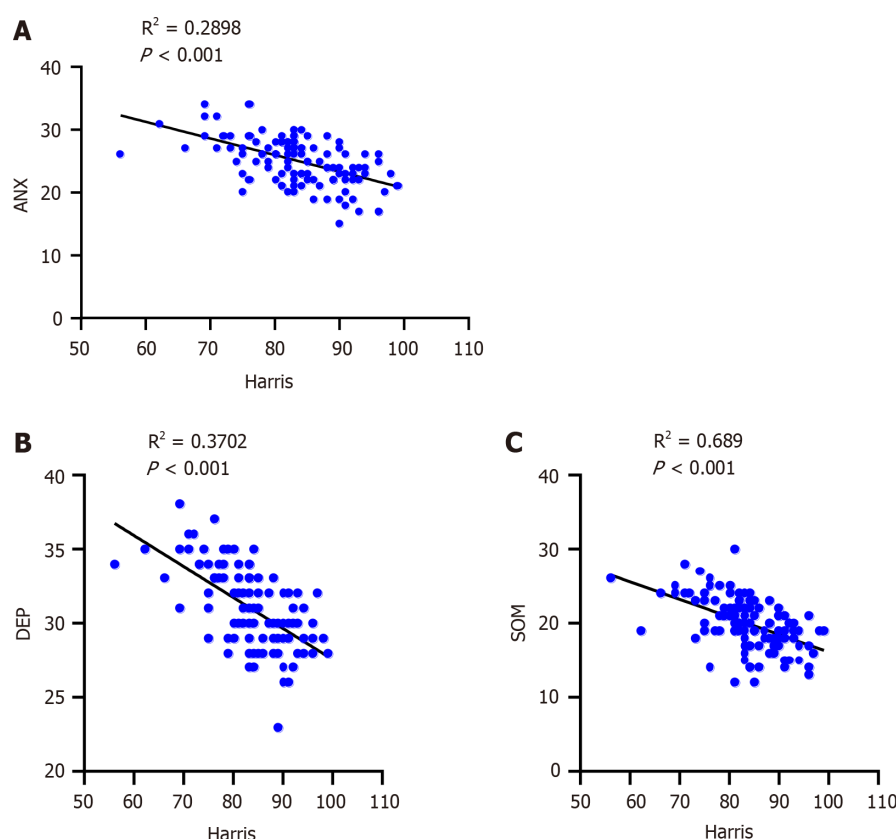


Figure 2 Correlation between Harris score and anxiety, depression, somatization. A: Correlation between Harris score and anxiety; B: Correlation between Harris score and depression; C: Correlation between Harris score and somatization. ANX: Anxiety; DEP: Depression; SOM: Somatization.

affecting their postoperative prognosis. In addition, preoperative adverse psychological stimulation may weaken the activity of osteoblasts and inhibit bone formation in the patients, resulting in fracture malunion and hip instability, which seriously affect hip function and worsen prognosis[16].

We further analyzed the relationship between the influencing indicators and the Harris score and found that ANX, DEP, and SOM scores were moderately correlated with the Harris score ($r = -0.523, -0.625, -0.554$; respectively). In other words, the higher the degree of anxiety, depression, and somatization in elderly patients with FNF, the lower and worse the Harris score and prognosis, respectively. The Harris scale evaluates postoperative hip pain, function, deformity, and range of motion. A score of < 80 was associated with a poor prognosis. The mechanisms by which anxiety, depression, and somatization affect the prognosis of elderly patients with FNF are not fully understood. A possible reason for this is that when elderly patients with FNF experience anxiety, depression, and physical disorders, their fracture injury can cause increased central excitability and change their somatic visceral and psychological state, thus deepening and consolidating their traumatic memory, and it can significantly enhance their subjective pain and slows their postoperative recovery process[17]. Xu *et al*[18] showed that perioperative anxiety and depression aggravate postoperative pain. Pain includes sensation caused by a nociceptive stimulus on the body and the response of the body to the nociceptive stimulus, which is often accompanied by intense emotional changes. Pain, anxiety, and depression can coexist and influence each other[19]. Lim *et al*[20] showed that poor psychological resilience in elderly patients undergoing hip fracture surgery hinders postoperative recovery of physical function. After conducting this study, we found that three indicators (anxiety, depression, and somatization) in the preoperative psychological stress state correlated significantly with the short-term prognosis of elderly patients with FNF. Therefore, we suggest that clinicians should pay attention to patients with preoperative ANX scores of ≥ 24.5 points, DEP scores of ≥ 32.5 points, and high SOM scores and be alert to the occurrence of poor short-term prognosis. Therefore, more targeted interventions are required. However, this study has some limitations. First, this was a retrospective study that relied on existing data and information, and the accuracy and completeness of these data are difficult to guarantee. Therefore, inaccurate or incomplete data may lead to bias or misleading research results. In addition, because the data are historical, retrospective studies are often unable to determine causation, which limits the reliability and validity of study conclusions. Therefore, the results of this study need to be further verified by randomized controlled studies to enhance the reliability of the results.

CONCLUSION

Preoperative ANX, DEP, and SOM scores correlated with a poor short-term prognosis in elderly patients with FNF and

warrant consideration. Clinicians should pay attention to emotional changes in patients during surgical and related treatment of elderly patients with FNF. Anxiety, depression, and somatization experienced by patients can be alleviated through relevant interventions to enhance surgical and postoperative trauma repair effects.

FOOTNOTES

Author contributions: Fu WH and Hu ZL designed the research, they contributed equally to this manuscript; Liao YJ, Chen RJ, and Qiu JB collected information and data; Que WT, Wang WT, and Li WH performed statistical analysis; Lan WB supervised the study and revised the manuscript for important intellectual content; and all authors read and approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Longyan First Affiliated Hospital of Fujian Medical University, Approval No. 2020(90).

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

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

Data sharing statement: The data used in this study can be obtained from the corresponding author upon request.

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Che XX

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Retrospective Study

Clinical effect of acupuncture at ghost points combined with fluoxetine hydrochloride on mild-to-moderate depression

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Radwan E, Palestine

Received: February 28, 2024

Revised: April 23, 2024

Accepted: May 9, 2024

Published online: June 19, 2024

Processing time: 112 Days and 2.1 Hours



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Abstract

BACKGROUND

Depression is a common, chronic, and recurrent mood disorder that has become a worldwide health hazard. Fluoxetine hydrochloride, a common treatment method, can inhibit 5-hydroxytryptamine (5-HT) recycling in the presynaptic membrane; however, the efficacy of a single drug is inadequate. At present, mild-to-moderate depression can be treated with acupuncture of ghost caves, but the clinical curative effect of combined therapy with fluoxetine hydrochloride has not

been sufficiently reported.

AIM

To evaluate the clinical effect of acupuncture at ghost points combined with fluoxetine hydrochloride in the treatment of mild-to-moderate depression.

METHODS

This retrospective study included 160 patients with mild-to-moderate depression who were admitted to Shanghai Hospital of Integrated Traditional Chinese and Western Medicine, Affiliated to Shanghai University of Traditional Chinese Medicine, between January 2022 and June 2023. Patients were separated into a single-agent group (fluoxetine hydrochloride treatment, $n = 80$) and a coalition group (fluoxetine hydrochloride treatment combined with acupuncture at ghost points, $n = 80$). Pre-treatment symptoms were recorded, and the clinical curative effect and adverse reactions [Asberg Antidepressant Side Effects Scale (SERS)] were assessed. Depression before and after treatment [Hamilton Depression Scale (HAMD)-24], neurotransmitter levels [5-HT, norepinephrine (NE), dopamine (DA)], oxidative stress indicators [superoxide dismutase (SOD), malondialdehyde (MDA)], and sleep quality [Pittsburgh Sleep Quality Index (PSQI)] were compared.

RESULTS

The total efficacy rate was 97.50% in the coalition group and 86.25% in the single-agent group ($P < 0.05$). After 2, 4, 6, and 8 wk of treatment, the HAMD, self-rating depression scale, and SERS scores of the coalition and single-agent groups decreased compared with pre-treatment, and the decrease was more significant in the coalition group ($P < 0.05$). After 8 wk of treatment, the levels of NE, DA, 5-HT, and SOD in the coalition and single-agent groups increased, while the levels of MDA decreased; the increases and decrease in the coalition group were more significant ($P < 0.05$). The PSQI scores of the coalition and single-agent groups decreased, and the decrease was more significant in the coalition group ($P < 0.05$).

CONCLUSION

Acupuncture at ghost points combined with paroxetine tablets can safely improve depressive symptoms and sleep disorders, regulate neurotransmitter levels, and reduce stress responses in patients with mild-to-moderate depression.

Key Words: Depression; Prick; Fluoxetine hydrochloride; Curative effect; Depressive symptoms; Oxidative stress index

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Core Tip: Depression is a common psychiatric disease that can manifest as low mood, decreased interest, and energy fatigue. The rates of suicide and self-harm associated with depression are very high. In this study, we found that, compared with fluoxetine treatment alone, acupuncture at ghost points combined with paroxetine hydrochloride can improve mild-to-moderate depression and sleep disturbance in patients, regulate neurotransmitter levels, reduce stress responses, and improve safety.

Citation: Wang Y, Lu Q, Penpat I, Wu J, Abulikemu D, Zeng FC, Huang JY, Hu ZH. Clinical effect of acupuncture at ghost points combined with fluoxetine hydrochloride on mild-to-moderate depression. *World J Psychiatry* 2024; 14(6): 848-856

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/848.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.848>

INTRODUCTION

Depression is a mental and psychological disease characterized by persistent low mood, slow thinking, decline in cognitive function, decreased volitional activity, and physical symptoms, and it is an important cause of global mental disability[1,2]. Depression is expected to become the world's largest disease threatening human physical and mental health by 2030[3]. Selective serotonin reuptake inhibitor antidepressants including fluoxetine hydrochloride are currently one of the typical drug types used in the clinical treatment of depression[4]. They act on the synapses of the central nervous system to inhibit the reuptake of serotonin by the presynaptic membrane, thereby achieving therapeutic effects. However, satisfactory results are difficult to achieve owing to shortcomings, such as a long period of stable plasma concentration, a narrow antidepressant spectrum, and obvious side effects[5].

Depression aligns with the traditional Chinese medicine 'depressive syndrome' category and is closely associated with the Yang-deficiency constitution. Based on the theory that Yang deficiency causes depression, some studies have verified the feasibility of treating depression with Yang support[6,7]. Acupuncture plays a unique role in the treatment of diseases and is a common therapy in traditional Chinese medicine. Current clinical trials on acupuncture's effects on brain

mechanisms of the central nervous system have aroused medical attention. Studies have shown that acupuncture plays a significant role in protecting neurons[8]. In addition, domestic and foreign doctors have achieved remarkable results in the clinical treatment of patients with depression using acupuncture. Its mechanism of action is related to the regulation of the cortical striatum reward/motivation circuit in the brains of patients with depression. Studies have shown that acupuncture combined with drug treatment for depression can improve the depressive state and physical symptoms of patients with depression. Compared with drug use alone, acupuncture combined with drug treatment has been shown to improve efficacy, reduce adverse reactions, and reduce drug dose[9]. Acupuncture at effective thirteen ghost points is used in traditional Chinese medicine to treat emotional diseases. In recent years, acupuncture has been commonly used to treat intractable insomnia, Alzheimer's disease, vascular dementia, and other brain diseases, and can effectively alleviate conditions with significant curative effects[10,11]. However, few reports exist on the clinical effects of acupuncture at ghost points combined with fluoxetine hydrochloride in mild-to-moderate depression. This study aimed to explore the clinical effects of acupuncture at ghost points combined with fluoxetine hydrochloride on mild-to-moderate depression to provide a reference for clinical treatment.

MATERIALS AND METHODS

Participants

This retrospective study included 160 patients with mild-to-moderate depression who were admitted to Shanghai Hospital of Integrated Traditional Chinese and Western Medicine, Affiliated to Shanghai University of Traditional Chinese Medicine, between January 2022 and June 2023. The diagnostic criteria for depression included core symptoms and additional symptoms[12]. Core symptoms were as follows: (1) Majority of time spent in a depressed state unaffected by external factors for > 2 wk; (2) Disinterest or inability to obtain pleasure from things that were once of interest or love; and (3) Regular feelings of tiredness and powerlessness. Additional symptoms were as follows: (1) Inattention; (2) Regular feelings of self-denial and lack of self-confidence; (3) Feelings of responsibility for mistakes with the concept of self-incrimination; (4) Thoughts of having no future; (5) Insomnia; (6) Regular suicidal tendencies and behavior; (7) Loss of appetite; and (8) Mild-to-moderate depression, namely a Hamilton Depression Scale-24 (HAMD-24) score of 7 to 24 points.

The inclusion criteria for this study were as follows: (1) Symptoms meeting the above diagnostic criteria; (2) No history of other antipsychotic drugs or hypnotic drugs before treatment; (3) Age of 18-70 years; and (4) Availability of complete data. The exclusion criteria were as follows: (1) Presence of severe, life-threatening organic lesions; (2) Presence of a malignant tumor, infection, or hemorrhage; (3) History of serious suicide attempts and behaviors; (4) Pregnancy or lactation; and (5) Presence of unhealed moxibustion site trauma skin lesions, local ulcers, red and swollen skin, or allergies. Based on the differences in intervention methods, patients were separated into single-agent and coalition groups ($n = 80$ cases each). No significant differences were identified in baseline data between the coalition and single-agent groups ($P > 0.05$) (Table 1).

Methods

The single-agent group received oral fluoxetine hydrochloride capsules (Lilai Suzhou Pharmaceutical Co., Ltd., Sinopharm Approval No.: J20170022). The specific method of administration was performed according to the physicians' advice. Oral administration of a 20 mg/d dose for 8 wk was recommended. The coalition group was based on single drug administration plus acupuncture at ghost points. Acupoint selection included ghost points "above the star": Shuigou, Shaoshang, Yinbai, Daling, and Shenmai. The operation method was as follows: The patient was placed in the supine position and underwent routine skin disinfection. A Hua Tuo card (0.25 mm in diameter) was used with a disposable stainless steel filiform needle (diameter, 0.25 mm; length, 40 mm) for acupuncture. The Shuigou point was obliquely punctured in the direction of the nasal septum, which should stimulate tears. The needle was then sequentially inserted into the Shaoshang, Yinbai, Daling, and Shenmai points with a strong needle sensation. Among them, the Shaoshang and Yinbai points were obliquely punctured from the outside to the nail angle at a depth of 0.1-0.2, and the Daling point was punctured directly with electric shock. The Shangxing point was punctured with a flat thorn at an acupuncture depth of 0.5-0.8 in using the extraction method. All acupuncture operators had equal training performing the standardized operation. Each treatment lasted 30 min and was administered once per day, 5 times per week. Four treatment cycles took place: One observation cycle comprised ten occurrences, and continuous treatment was administered for three cycles.

Survey tools

Clinical efficacy: To evaluate clinical efficacy in patients, the improvement rate of HAMD-24 scores was calculated prior to treatment and 8 wk after treatment to obtain the efficacy index. The efficacy index was calculated as follows: (HAMD-24 score pre-treatment-HAMD-24 score 8 wk after treatment)/HAMD-24 score pre-treatment $\times 100\%$. The efficacy index was categorized as follows: Clinical control, efficacy index $\geq 75\%$; obvious effect, $50\% \leq$ efficacy index $< 75\%$; effective, $25\% \leq$ efficacy index $< 50\%$; and ineffective, efficacy index $< 25\%$. The total effective rate was calculated as follows: (Effective + obvious + clinical control)/total disease $\times 100\%$. The efficacy evaluation was completed at 0, 2, and 8 wk.

Depressive symptoms: The HAMD-24[13] and self-rating depression scale (SDS)[14] were used to score depressive symptoms before and after treatment (2, 4, 6, and 8 wk after treatment). HAMD-24 scores were categorized as follows: Normal, scores of < 7 ; mild depression, scores of 7-16; moderate depression, scores of 17-23; severe depression, scores of 24-34; and further division of severe depression, scores of > 34 . With a total of 20 items in the scale, the SDS was

Table 1 Comparison of baseline data

Group	Sex		Age (yr)	Degree of depression		Duration of disease (yr)
	Male	Female		Mild	Moderate	
Coalition group (<i>n</i> = 80)	35	45	35.33 ± 9.06	46	34	2.41 ± 0.69
Single-agent group (<i>n</i> = 80)	37	43	36.16 ± 9.00	48	32	2.51 ± 0.72
χ^2/t	0.101		-0.587	0.103		-0.826
<i>P</i> value	0.751		0.558	0.748		0.410

categorized as follows [standard score = rough score × 1.25 (integer part)]: Normal, 25-49 points; mild depression, 50-59 points; moderate depression, 60-69 points; and severe depression, 70 points.

Neurotransmitter levels: Neurotransmitter levels were analyzed. Before treatment and 8 wk after treatment, 10 mL of fasting peripheral venous blood was extracted from patients in the two groups, and 5 mL was placed into a 4 °C centrifuge for centrifugation. The upper serum was absorbed using a pipette and divided into 0.6-mL EP tubes. Serum levels of norepinephrine (NE), 5-hydroxytryptamine (5-HT), and dopamine (DA) were measured using high-pressure liquid chromatography-electrochemistry (North Institute of Biotechnology, Beijing).

Oxidative stress index: To measure the oxidative stress index, another 5 mL blood sample was taken. After centrifugation of the supernatant, an enzyme-linked immunosorbent assay (Wuhan Bode Biotechnology Co., Ltd.) was used to detect malondialdehyde (MDA) and superoxide dismutase (SOD) levels.

Sleep quality: The Pittsburgh Sleep Quality Index (PSQI)[15] was used to evaluate sleep quality. The PSQI consists of 19 self-rating questions and 5 other rating questions. The total score ranges from 0 to 21 points, with 0-5 indicating very good sleep quality, 6-10 indicating good sleep quality, 11-15 indicating average sleep quality, and > 15 indicating poor sleep quality.

Adverse reactions: According to the Asberg Rating Scale for Side Effects (SERS)[16], the adverse reactions in the coalition and single-agent groups were evaluated before and after treatment (2, 4, 6, and 8 wk later). The SERS contains a total of 14 items and uses a 4-level scoring method (0-3 points). The total score ranges from 0 to 42 and is proportional to the degree of adverse reactions.

Statistical analysis

Data were analyzed using the IBM SPSS software (version 29.0). Counting variables are expressed as numbers and percentages, and continuous variables are reported as means ± SD. They were tested using χ^2 and *t* tests, respectively. *P* < 0.05 indicates statistical significance.

RESULTS

Clinical effect

The total efficacy rate was 97.50% in the coalition group and 86.25% in the single-agent group (*P* < 0.05) (Table 2).

Depressive symptom

Pre-treatment, the HAM-D-24 and SDS scores of the coalition and single-agent groups were not significantly different (*P* > 0.05). However, 2, 4, 6, and 8 wk after treatment, the HAM-D-24 and SDS scores of the coalition and single-agent groups decreased, with a more significant decrease in the coalition group (*P* < 0.05) (Figure 1).

Neurotransmitter levels

Pre-treatment, the 5-HT, DA, and NE levels were not significantly different among the coalition and single-agent groups (*P* > 0.05). However, 2, 4, 6, and 8 wk after treatment, the levels of 5-HT, DA, and NE increased in the coalition and single-agent groups, with more significant increases in the coalition group (*P* < 0.05) (Table 3).

Oxidative stress index

Pre-treatment, the MDA and SOD levels were not significantly different between the coalition and single-agent groups (*P* > 0.05). However, after 8 wk of treatment, SOD levels increased and MDA levels decreased, with more significant increase and decrease ranges in the coalition group (*P* < 0.05) (Table 4).

PSQI score

Pre-treatment, the PSQI scores were not significantly different between the coalition and single-agent groups (*P* > 0.05). After 8 wk of treatment, the PSQI scores of the coalition and single-agent groups decreased, with a more significant

Table 2 Comparison of clinical efficacy between the coalition and single-agent groups, <i>n</i> (%)					
Group	Clinical control	Remarkable	Effective	Invalid	Total effective rate (%)
Coalition group (<i>n</i> = 80)	28 (35.00)	32 (40.00)	18 (22.50)	2 (2.50)	78 (97.50)
Single-agent group (<i>n</i> = 80)	18 (22.50)	23 (28.75)	28 (35.00)	11 (13.75)	69 (86.25)
χ^2					6.782
<i>P</i> value					0.009

Table 3 Comparison of neurotransmitter levels between the two groups at pre-treatment and 8 wk after treatment						
Group	5-HT (ng/mL)		DA (pg/mL)		NE (pg/mL)	
	Pre-treatment	After 8 wk of treatment	Pre-treatment	After 8 wk of treatment	Pre-treatment	After 8 wk of treatment
Coalition group (<i>n</i> = 80)	95.81 ± 8.35	130.56 ± 16.39 ^a	122.59 ± 13.55	148.57 ± 16.34 ^a	8.83 ± 2.41	14.66 ± 2.77 ^a
Single-agent group (<i>n</i> = 80)	96.38 ± 9.05	119.25 ± 14.45 ^a	120.36 ± 12.85	133.55 ± 13.44 ^a	9.11 ± 1.96	12.14 ± 2.51 ^a
<i>t</i>	-0.421	4.628	1.068	6.354	-0.808	6.017
<i>P</i> value	0.674	< 0.001	0.287	< 0.001	0.420	< 0.001

^a*P* < 0.00001
5-HT: 5-hydroxytryptamine; DA: Dopamine; NE: Norepinephrine.

Table 4 Comparison of oxidative stress indexes between the two groups at pre-treatment and 8 wk after treatment				
Group	MDA (mmol/L)		SOD (U/mL)	
	Pre-treatment	After 8 wk of treatment	Pre-treatment	After 8 wk of treatment
Coalition group (<i>n</i> = 80)	12.21 ± 1.80	7.54 ± 1.02 ^a	55.55 ± 5.62	68.16 ± 6.75 ^a
Single-agent group (<i>n</i> = 80)	12.09 ± 1.77	8.80 ± 1.31 ^a	55.65 ± 5.70	61.10 ± 5.95 ^a
<i>t</i>	0.424	-6.762	-0.123	7.002
<i>P</i> value	0.672	< 0.001	0.902	< 0.001

^a*P* < 0.00001
MDA: Malondialdehyde; SOD: Superoxide dismutase.

decrease in the coalition group (*P* < 0.05) (Table 5).

SERS score

Pre-treatment, the SERS scores were not significantly different between the coalition and single-agent groups (*P* > 0.05); however, after 2, 4, 6, and 8 wk of treatment, the SERS scores of the coalition and single-agent groups decreased, with a more significant decrease in the coalition group (*P* < 0.05) (Table 6).

DISCUSSION

The clinical manifestations of mild-to-moderate depression mainly include inattention, persistently low mood, low self-evaluation, slow thinking activity, poor social adaptability, and listlessness. With disease aggravation, patients may experience mental symptoms, such as delusions and hallucinations[17]. In recent years, the incidence of depression has increased annually, placing a heavy burden on society and families. Paroxetine hydrochloride is a class of selective NE reuptake inhibitors that can be metabolized by the liver without metabolite activity and has a good antidepressant effect with few adverse reactions. It is commonly used to treat depression, but its single-drug effect is poor[18].

The ‘depression syndrome’ category of traditional Chinese medicine occurs because of congenital physical weakness or liver fire flourishing coupled with acquired emotional disorders, resulting in qi blockage, mental disorders, and a class of diseases. Clinical manifestations include depression, chest pain, and hypochondriac fullness. In the theory of traditional

Table 5 Comparison of Pittsburgh Sleep Quality Index scores between the two groups at pre-treatment and 8 wk after treatment

Group	Pre-treatment	After 8 wk of treatment
Coalition group (<i>n</i> = 80)	14.80 ± 3.23	5.38 ± 1.70 ^a
Single-agent group (<i>n</i> = 80)	14.85 ± 3.16	7.53 ± 2.09 ^a
<i>t</i>	-0.099	-7.130
<i>P</i> value	0.921	< 0.001

^a*P* < 0.00001.**Table 6 Comparison of Scale for Side Effects scores between the two groups at pre-treatment and 8 wk after treatment**

Group	Pre-treatment	After treatment			
		After 2 wk	After 4 wk	After 6 wk	After 8 wk
Coalition group (<i>n</i> = 80)	10.75 ± 2.51	8.89 ± 2.39 ^b	8.16 ± 2.10 ^b	6.75 ± 2.13 ^b	5.11 ± 1.69 ^b
Single-agent group (<i>n</i> = 80)	10.86 ± 2.32	9.85 ± 2.11 ^a	9.18 ± 2.03 ^b	7.75 ± 2.00 ^b	6.82 ± 1.84 ^b
<i>t</i>	-0.294	-2.702	-3.136	-3.062	-6.116
<i>P</i> value	0.769	0.008	0.002	0.003	< 0.001

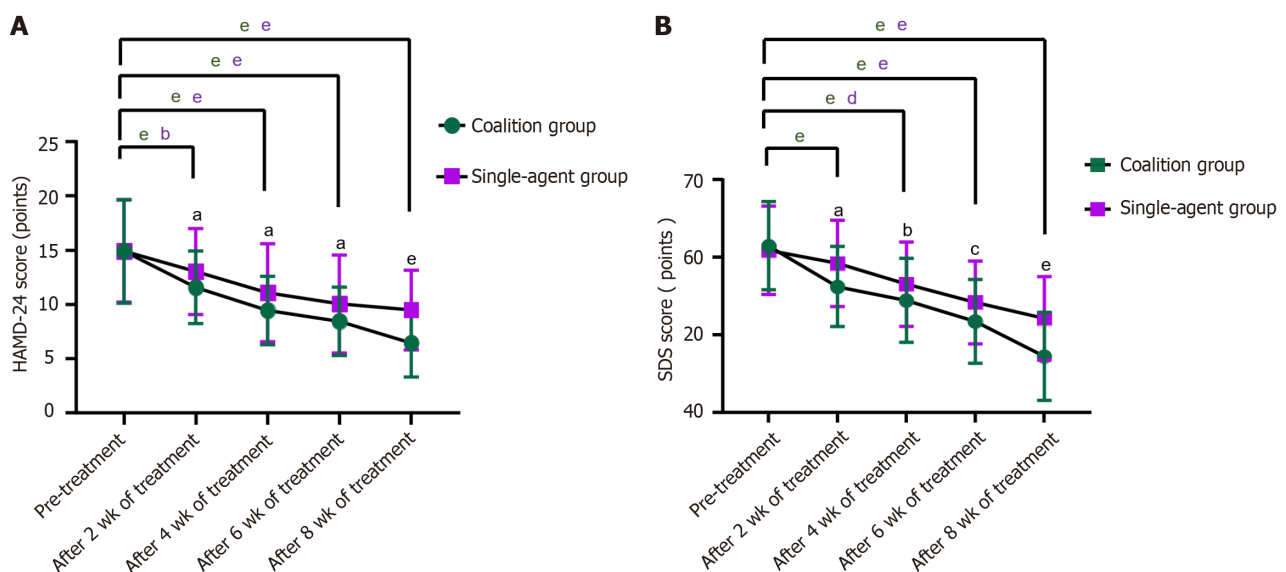
^a*P* < 0.01.^b*P* < 0.00001.

Figure 1 Hamilton Depression Scale-24 and self-rating depression scale scores in the two groups before and after treatment (2, 4, 6, 8 wk). A: Hamilton Depression Scale-24 scores in the two groups before and after treatment (2, 4, 6, and 8 wk); B: Self-rating depression scale scores in the two groups before and after treatment (2, 4, 6, and 8 wk). HAMD-24: Hamilton Depression Scale-24; SDS: Self-rating depression scale. ^a*P* < 0.05, ^b*P* < 0.01, ^c*P* < 0.001, ^d*P* < 0.0001, ^e*P* < 0.00001.

Chinese medicine, qi and blood are important components of the human body which maintain the operation of the body's qi machine. Internal injury of the seven emotions relates to a weak zangqi element, and the stagnation of liver qi and loss of temper lead to the imbalance of Yin and Yang in Zangfu organs, qi, and blood, resulting in mental health disorders and similar diseases of emotional depression[19]. Acupuncture at ghost points clears channels and collaterals, regulates qi, harmonizes Yin and Yang, and improves depressive symptoms[20]. The Shangxing point selected in this study is located in the governor vessel, which can awaken the brain and tranquilize the mind. Shaoshang is the well point of the lung meridian, and Yinbai is the well point of the spleen meridian. Acupuncture can not only drain the lung and transport the spleen but can also awaken the spirit and open the orifices. Shenmai is the Jinmen point of the bladder meridian, which is the same as the lung meridian qi and blood. Therefore, acupuncture can stimulate the meridian qi of

the human body and regulate the function of qi and blood. ‘Lingshu Meridian’ records that changes in the Yangming meridian change the spirit and emotion. Qi and blood are easy to move, and the spirit is not separated from qi and blood. The thirteen ghost acupoints were specially used to wake up the spirit, open the orifices, clear the heart, relieve depression, regulate qi, and tranquilize the mind[21]. Acupuncture at the Guixin and Daling point broadens the chest and regulates qi to promote blood circulation and dredge collaterals. It may be combined with acupuncture at the Laogong point of the heart to purge fire, clear the heart, and calm the mind. Loss of transportation and transformation of the spleen leads to phlegm and dampness. Acupuncture at the Guilei Yinbai point helps the transportation and transformation of the spleen to invigorate it, remove dampness, and reduce turbidity. Acupuncture at the Guigong Shuigou and Guitang Shangxing on the head can dredge the governor vessel and regulate the mind, open the orifices, and relieve depression [22].

In this study, the total efficacy rate was 97.50% in the coalition group and 86.25% in the single-agent group ($P < 0.05$), suggesting that acupuncture combined with paroxetine hydrochloride tablets had a better effect on mild-to-moderate depression. After treatment, the HAMD, SDS, and PSQI scores in the coalition group were lower than those in the single-agent group ($P < 0.05$), suggesting that acupuncture at ghost points combined with paroxetine hydrochloride tablets can significantly improve depressive symptoms and sleep disorders in patients. Antidepressants are usually accompanied by adverse reactions, such as drowsiness, dizziness, headache, and gastrointestinal reactions. Studies have shown that acupuncture may not only accelerate the onset time of antidepressants but also improve the overall efficacy and reduce adverse reactions[23,24]. In this study, the total SERS scores of the coalition group after treatment were lower than those of the single-agent group ($P < 0.05$), suggesting that acupuncture at ghost points can safely reduce the adverse reactions caused by paroxetine hydrochloride tablets.

The 5-HT content in the cerebral cortex and synapses is very high and can promote neuronal differentiation. A lower level of 5-HT correlates with more severe depressive symptoms and worse prognosis[25]. DA is a catecholamine neurotransmitter present in the nerve tissues and body fluids. When people are happy, relaxed, pleasant, comfortable, and enjoyable, DA secretion increases significantly. Poor function of the DA system in patients with depression directly damages the plasticity of the hippocampus-frontal cortex synapses, leading to emotional regulation and cognitive dysfunction[26]. NE is a common neurotransmitter affecting various regions of the brain. It can regulate arousal and stress responses by regulating synaptic afferent activity and reducing afferents of interfering stimuli. It has been reported that depression is closely related to disorders of brain 5-HT and NE activity, and increasing the levels of NE and 5-HT in the brain is a good strategy to treat depression[27]. In a study on depression, Wang *et al*[28] found that NE and 5-HT activity in the brains of patients was significantly increased after drug intervention. And it showed that similar to the effect of the positive drug (fluoxetine) on the regulation of NE and 5-HT content, Xiaoyao-jieyu-san could effectively increase the NE and 5-HT content in the brain tissue of PSD rats. Studies have shown that acupuncture at ghost points can excite the ascending nerve activation system and promote the production of neurotransmitters, such as 5-HT, DA, and NE. It can further regulate the excitation and inhibition processes of the cerebral cortex through the nerve-endocrine-immune system; thus, various neurotransmitters between synapses can be balanced. Acupuncture at ghost points can simultaneously enhance stress, promote adrenal secretion, and improve mental symptoms[29]. SOD is an enzyme that scavenges free oxygen radicals, and MDA is a product of peroxidation. The expression levels of both reflect the degree of lipid peroxidation in the body and the ability of the body to scavenge free oxygen radicals[30]. After 8 wk of treatment, the levels of NE, 5-HT, DA, and SOD in the coalition and single-agent groups increased, while the level of MDA decreased. The increase and decrease in the coalition group were more significant ($P < 0.05$), suggesting that paroxetine hydrochloride tablets combined with acupuncture at ghost points can regulate the levels of neurotransmitters in patients with mild-to-moderate depression and reduce the oxidative stress response. This study still has some limitations. For example, this study is a single-center study with a single sample source. Therefore, its generalizability to a wider population, including different ethnic and cultural backgrounds, is not clear. In the future, multi-center studies will be carried out to expand the sample size for further exploration.

CONCLUSION

In summary, treatment with paroxetine hydrochloride tablets combined with acupuncture at ghost points in patients with mild-to-moderate depression can safely and significantly improve depressive symptoms and sleep disorders, regulate the levels of neurotransmitters, and reduce oxidative stress responses.

FOOTNOTES

Author contributions: Wang Y and Lu Q designed and completed the research; Penpat I, Wu J, Abulikemu D, Zeng FC, and Huang JY collected and analyzed the information and data; Hu ZH designed and reviewed the study.

Supported by the General Program of Shanghai Science and Technology Commission on Medical Innovation Research, No. 21Y11923500; the Second Round of the “National Medical Strong and Excellent” Three-Year Action Plan (2022-2024) of the Hongkou District of Shanghai Traditional Chinese Medicine Schools and Characteristic Technology Inheritance Support Construction Project, No. HKGYQYXM-2022-17; and the Shanghai Culture and Tourism Bureau.

Institutional review board statement: The study was approved by the Ethics Committee of the Shanghai Hospital of Integrated

Traditional Chinese and Western Medicine, Affiliated to Shanghai University of Traditional Chinese Medicine, No. 2021-053-1.

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

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

Data sharing statement: The clinical data used in this study can be obtained from the corresponding author upon request.

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Che XX

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Retrospective Study

Clinical intervention effect of Xuefu Zhuyu decoction on chronic heart failure complicated with depression

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Arslan G, Türkiye

Received: February 28, 2024

Revised: May 6, 2024

Accepted: May 8, 2024

Published online: June 19, 2024

Processing time: 112 Days and 2 Hours



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Abstract

BACKGROUND

The diagnosis and treatment of depression in patients with chronic heart failure (CHF) is challenging, with no ideal treatment at present.

AIM

To analyze the clinical intervention effect of Xuefu Zhuyu decoction (XFZYD) on CHF complicated with depression.

METHODS

The study cohort comprised 116 patients with CHF complicated with depression who received treatment from July 2020 to July 2023, of which 55 received Western medicine (control group) and 61 received XFZYD (research group). Data on clinical effectiveness, traditional Chinese medicine (TCM) syndrome score, cardiac function, negative emotions, and serum inflammatory factors, were collected for comparative analyses.

RESULTS

Compared with the control group, the research group had an evidently higher total effective rate. Furthermore, there were marked reductions in TCM symptom score, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, Self-Rating Depression Scale, Hamilton Depression Scale, high-sensitivity C-reactive protein, monocyte chemoattractant protein-1, and matrix metalloproteinase-9 in the research group after treatment, and these were lower than the corresponding values in the control group. Left ventricular ejection fraction was increased and higher in the research group compared with the control group after treatment.

CONCLUSION

Our findings conclusively proved that XFZYD was considerably superior to Western medicine for treating CHF complicated with depression because it significantly alleviated patients' symptoms, improved cardiac function, relieved negative emotions, and reduced the levels of serum inflammatory factors.

Key Words: Xuefu Zhuyu decoction; Chronic heart failure; Depression; Cardiac function; Negative emotions

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Core Tip: Chronic heart failure (CHF) is a hemodynamic disorder that leads to systolic and diastolic dysfunction and increases the risk of diabetes and chronic kidney disease. Additionally, the risk of depression in patients with CHF can reach up to 60%, and the diagnosis and treatment of depression in this patient population is challenging because there is no ideal therapy for this comorbidity. This study comparatively analyzed the clinical effects of Xuefu Zhuyu decoction (XFZYD) vs Western medicine in patients with CHF complicated with depression from the perspectives of clinical efficacy, traditional Chinese medicine symptom score, cardiac function, negative emotions, and serum inflammatory factor levels. We found that the clinical efficacy of XFZYD was significantly higher than Western medicine for treating CHF complicated with depression and significantly reduced patients' symptoms, improved cardiac function, alleviated negative emotions, and inhibited serum inflammatory factors. Therefore, XFZYD is highly beneficial for improving the efficacy and clinical outcomes of patients with CHF complicated with depression.

Citation: Wang Y, Wang J, Lv W, Chen H, Yang Q, Zhang Y, Guo R, Ma XL, Zhang QY. Clinical intervention effect of Xuefu Zhuyu decoction on chronic heart failure complicated with depression. *World J Psychiatry* 2024; 14(6): 857-865

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/857.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.857>

INTRODUCTION

Chronic heart failure (CHF) is a cardiovascular disease with high prevalence and a high frequency of hospitalization and death. CHF symptoms include fatigue, dyspnea, fluid retention, and poor exercise tolerance[1,2]. Because CHF is a hemodynamic disorder, it may lead to systolic and diastolic dysfunction and increase the risk of diabetes and chronic kidney disease[3]. Additionally, the risk of depression in CHF can reach 60%, and it has been associated with worsening patient conditions, particularly in older adults[4,5]. The cause of depression in CHF patients may be related to factors such as limited activities of daily living and functional symptoms, like immobility[6]. The comorbidity mechanism of CHF combined with depression is related to inflammatory overreaction and abnormal cardiac autonomic control and regulation[7]. The diagnosis and treatment of depression in patients with CHF are challenging, and there is currently no ideal treatment for this comorbidity[8,9]. Thus, solving the abovementioned issues will be of great value in improving the treatment effectiveness and clinical outcomes of patients with CHF complicated with depression.

There applications of traditional Chinese medicine (TCM) therapy for patients with CHF complicated with depression are increasing. Cai *et al*[10] reported that the practice of Tai Chi as a Chinese medicine exercise therapy by patients with CHF complicated with depression significantly alleviated their negative emotions. According to Wang *et al*[11], Buxin Yiqi decoction, as a TCM therapy, effectively reduced symptoms in patients with CHF and enhanced their prognosis, with a lower risk of adverse reactions compared with Western medicine therapy. Collectively, these findings indicate the high therapeutic potential of TCM therapy for patients with CHF complicated with depression. Xuefu Zhuyu decoction (XFZYD) is a Chinese herbal medicine that was introduced in the Qing Dynasty to regulate qi and disperse stagnation. It is composed of various Chinese herbs, including *Poria cocos*, *Paeonia lactiflora*, ginger, *Atractylodes macrocephala*, *Radix Paeoniae Rubra*, peach kernel, and *Fructus Aurantii*[12]. This prescription is used for treating angina pectoris, exerting positive effects on symptom relief, blood lipid metabolism, and quality of life[13]. TCM classifies CHF complicated with depression in the categories of chest obstruction and stagnation syndrome, which mainly manifests as blood stasis syndrome, with etiology associated with blood stasis obstruction of the heart pulse, stagnation of qi activity, and prolonged qi stagnation[14,15]. Therefore, CHF treatment is based on the principle of activating blood, dissolving stasis, regulating qi, and relieving depression, with XFZYD being the best choice.

Given the current scanty research on the therapeutic effect of XFZYD in patients with CHF complicated with depression, we performed this study to confirm the clinical effectiveness of this TCM therapy in such patients.

MATERIALS AND METHODS

Patients and general data

We enrolled 116 patients with CHF complicated with depression who received treatment at Cangzhou Central Hospital, China, between July 2020 and July 2023. The control group ($n = 55$) was administered Western medicine, and the research group ($n = 61$) was treated with XFZYD.

Criteria for patient enrollment and exclusion

All patients met the diagnostic criteria for CHF[16], with the syndrome of blood stasis and qi stagnation diagnosed by referring to the Guidelines for the Diagnosis and Treatment of Common Internal Diseases in Chinese Medicine[17]. The inclusion criteria were New York Heart Association (NYHA) classification grade II–III and TCM symptoms of depression, impatience, headache, insomnia, forgetfulness, pain in the chest and hypochondrium, chills or fever in a certain part of the body, a dark purple tongue or a tongue with petechiae and ecchymosis, and a stringy or uneven pulse. The exclusion criteria were as follows: use of other TCM decoctions 1 wk prior to enrollment or antidepressant medications within 1 month of enrollment; coagulation or immune dysfunction; uncontrollable hypertension and hyperglycemia; severe heart failure, severe ventricular arrhythmia, or constrictive pericarditis; other organ dysfunction; history of heart surgery; history of mental illness; infectious or blood system diseases; pregnancy or lactation; and incomplete clinical data.

Treatment methods

All patients received conventional treatment according to the European Society of Cardiology 2016 Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, as well as conventional psychological care interventions [18].

The control group was treated with Western medicine (flupentixol and melitracen tablets administered in the morning and at noon, one tablet at a time). The research group received XFZYD. The prescription comprised 12 g peach kernel; 9 g each of *Carthamus tinctorius* L., angelica, *Radix Rehmanniae*, and *Achyranthis Bidentatae*; 10 g each of chuanxiong rhizome and *Platycodon grandiflorus*; 6 g each of *Radix Paeoniae Rubra*, *Fructus Aurantii*, and licorice; and 15 g of *Radix Bupleuri*. The above components were boiled in 500 mL of clear water and simmered to reduce the volume to 400 mL. The drug was taken warm, with 200 mL in the morning and evening, respectively, for a course of treatment of 4 weeks. Both groups were treated for two consecutive courses.

Endpoints

Efficacy: The therapeutic effectiveness of both groups was observed and recorded. Marked effectiveness was defined as the basic or complete disappearance of clinical symptoms, including the evaluation of cardiac function as NYHA grade I or an improvement by more than two grades and a $\geq 70\%$ reduction in the TCM symptom score. Effectiveness was defined as an obvious improvement of clinical symptoms, including an improvement of cardiac function by one grade but not by up to two grades, and a reduction of 30%–70% in the TCM symptom score. Ineffectiveness was defined as no significant improvement or deterioration of clinical symptoms, improvement of cardiac function by less than one grade or worsening of cardiac function, and a reduction of $< 30\%$ in the TCM symptom score or a higher score than before treatment. The total effective rate was the sum of the marked effectiveness rate and effectiveness rate.

TCM symptom score: All patients were scored by the same physician before and after treatment for seven symptoms: Depression, frequent sighing, palpitations, fatigue, shortness of breath and weakness, pale complexion, and cold hands and feet, with a total score of 7–21, proportional to the symptoms and signs.

Cardiac function: The left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) were measured by echocardiography before and after treatment.

Negative emotions: The depressive mood of the patients was assessed using the Self-Rating Depression Scale (SDS), which comprises 20 items with a score of 0–80. Patients' depression was also evaluated using the Hamilton Depression Scale (HAMD), which comprises 17 items, with a score of 0–68. For both the SDS and HAMD, the higher the score, the more serious the depression.

Serum inflammatory factors: We collected 5 mL of venous blood before and after treatment. The serum was obtained after centrifugation and used to determine the levels of high-sensitivity C-reactive protein (hs-CRP), monocyte chemoattractant protein-1 (MCP-1), and matrix metalloproteinase-9 (MMP-9) by enzyme-linked immunosorbent assay.

Statistical analysis

Continuous variables were described as mean \pm SD, with intergroup and intragroup comparisons performed using *t*-test and paired *t*-test, respectively. Categorical variables were described as numbers and percentages, and intergroup comparisons were performed using χ^2 test. SPSS v24.0 software was used for statistical analysis. *P* values < 0.05 were considered statistically significant.

Table 1 General information				
Indicators	Control group (n = 55)	Research group (n = 61)	χ^2/t -test	P value
Sex (male/female)	35/20	37/24	0.109	0.741
Age (yr)	58.00 ± 5.97	58.77 ± 7.06	0.631	0.530
CHF course (yr)	3.89 ± 0.66	3.84 ± 0.82	0.359	0.720
NYHA classification (II/III)	31/24	35/26	0.012	0.912
Depression course (months)	4.53 ± 0.77	4.67 ± 0.94	0.872	0.385
Depression degree (mild/moderate)	17/38	20/41	0.047	0.829

CHF: Chronic heart failure; NYHA: New York Heart Association.

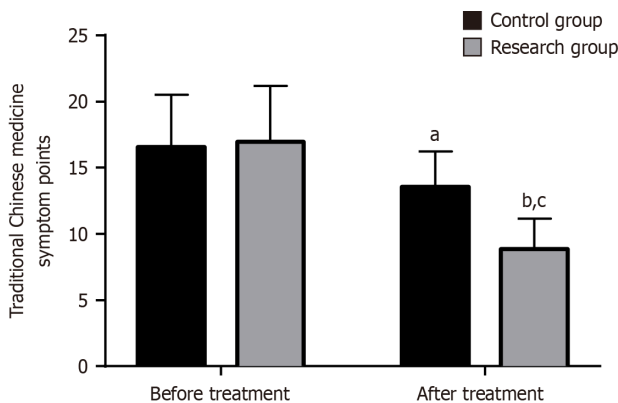


Figure 1 Traditional Chinese medicine symptom score. ^a $P < 0.05$ and ^b $P < 0.01$ vs before treatment; ^c $P < 0.05$ vs control group.

RESULTS

General information

The two groups were similar in sex, age, CHF course, NYHA grade, and the course and degree of depression ($P > 0.05$; Table 1).

Clinical effectiveness

The total effective cases in the control and research groups were 43 and 58, respectively, indicating a significantly higher total effective rate in the research group compared with the control group ($P < 0.05$; Table 2).

TCM symptom score

We calculated the TCM symptom scores of both groups before and after treatment. There were no significant differences between groups before treatment ($P > 0.05$). However, the scores decreased significantly ($P < 0.05$) after treatment in both groups, particularly in the research group (Figure 1).

Cardiac function

The main evaluation indices of cardiac function were LVEF, LVEDD, and LVESD. The two groups did not differ markedly in the pretreatment levels of these three indices ($P > 0.05$). However, LVEF significantly increased ($P < 0.05$) in both groups after treatment, with an even higher increase in the research group. Furthermore, LVEDD and LVESD were significantly reduced ($P < 0.05$) after treatment and were lower in the research group than in the control group (Figure 2).

Negative emotions

We used the SDS and HAMD scales to evaluate changes in depressive mood in the two groups. No notable intergroup differences were identified in the two scale scores before treatment ($P > 0.05$). A significant reduction ($P < 0.05$) was observed in SDS and HAMD scores in both groups after treatment, and these were more significantly decreased in the research group compared with the control group (Figure 3).

Serum inflammation

We measured the levels of the major serum inflammatory factors hs-CRP, MCP-1, and MMP-9. There were no significant intergroup differences before treatment ($P > 0.05$). After treatment, both the research and control groups showed

Table 2 Clinical efficacy

Indicators	Control group (n = 55)	Research group (n = 61)	χ^2	P value
Marked effectiveness	16 (29.09)	22 (36.07)		
Effectiveness	27 (49.09)	36 (59.02)		
Ineffectiveness	12 (21.82)	3 (4.92)		
Total effective rate	43 (78.18)	58 (95.08)	7.337	0.007

Results are presented as *n* (%).

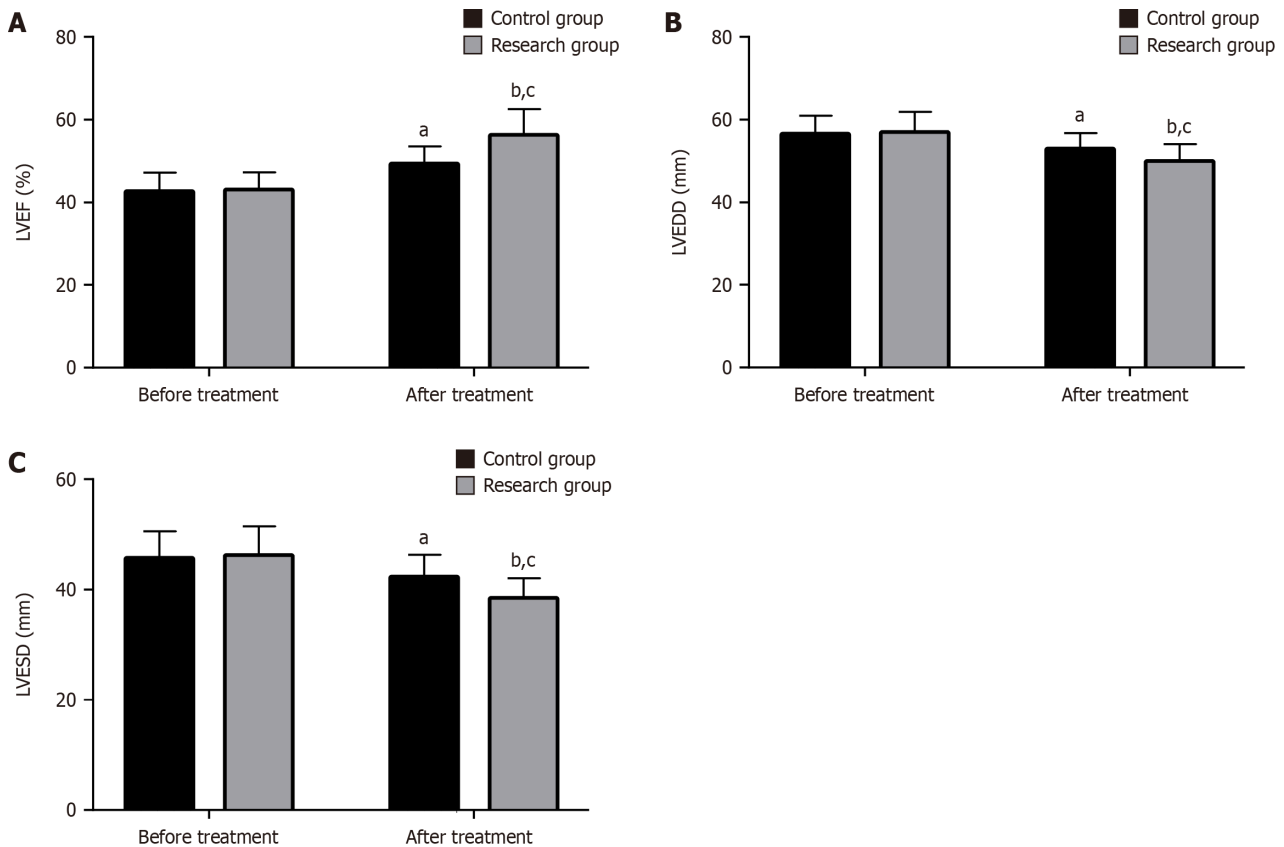


Figure 2 Cardiac function. A: Left ventricular ejection fraction in both groups increased significantly after treatment; B: Left ventricular end-diastolic diameter in both groups decreased significantly after treatment; C: Both groups showed significantly reduced Left ventricular end-systolic diameter after treatment. ^a*P* < 0.05 and ^b *P* < 0.01 vs before treatment; ^c*P* < 0.05 vs control group. LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter.

markedly lowered hs-CRP, MCP-1, and MMP-9 Levels, and the levels in the research group were lower than those in the control group (*P* < 0.05; Figure 4).

DISCUSSION

Depression is a debilitating mental illness characterized by persistent low spirits, reduced enthusiasm for daily life, and a dulled ability to experience happiness[19]. The disease is common in patients with CHF and is not only harmful to patient recovery but also increases the risk of suicide[20]. This study analyzed the clinical intervention effect of XFZYD on CHF complicated with depression, with the aim of improving the curative effect in such patients.

The total effective rate in the research group was 95.08%, which was significantly higher than that of the control group (78.18%), indicating that the use of XFZYD in patients with CHF and depression is conducive to a significant improvement in clinical efficacy. The peach kernel used in XFZYD has the effect of expelling blood stasis, promoting stagnation, and moistening dryness[21]. *Carthamus tinctorius* L., *Radix Paeoniae Rubra*, and *Achyranthes bidentata* promote blood circulation, eliminate blood stasis, and relieve pain[22]. *Platycodon grandiflorus* and *Fructus Aurantii*, which are responsible for regulating ascending and descending qi, respectively, alleviate mental depression and promote qi

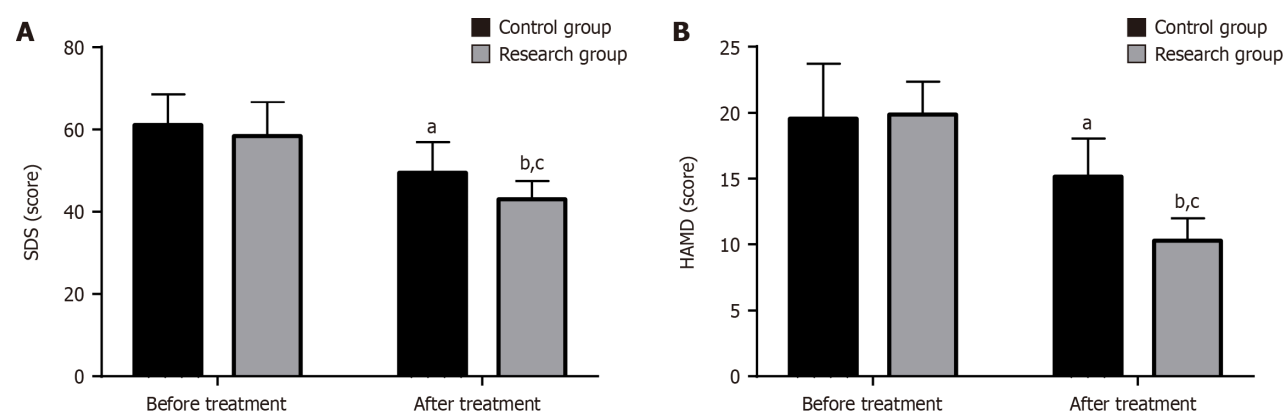


Figure 3 Negative emotions. A: Both groups had significantly reduced Self-Rating Depression Scale scores after treatment; B: Both groups had significantly reduced Hamilton Depression Scale scores after treatment. ^a $P < 0.05$ and ^b $P < 0.01$ vs before treatment; ^c $P < 0.05$ vs control group. HAMD: Hamilton Depression Scale; SDS: Self-Rating Depression Scale.

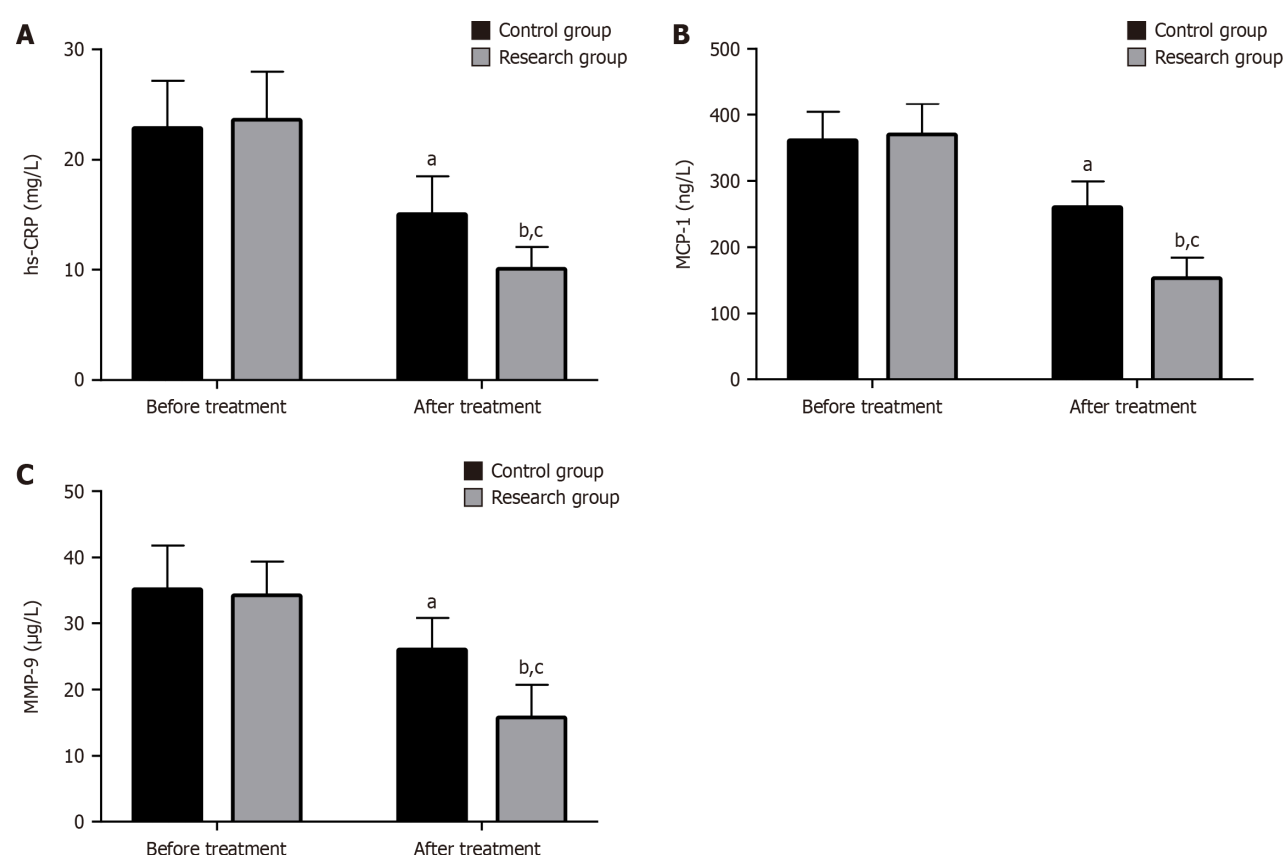


Figure 4 Serum inflammatory factors. A: Levels of high-sensitivity C-reactive protein in both groups decreased significantly after treatment; B: Levels of monocyte chemoattractant protein-1 in both groups decreased significantly after treatment; C: Levels of matrix metalloproteinase-9 in both groups decreased significantly after treatment. ^a $P < 0.05$ and ^b $P < 0.01$ vs before treatment; ^c $P < 0.05$ vs control group. hs-CRP: High-sensitivity C-reactive protein; MCP-1: Monocyte chemoattractant protein-1; MMP-9: Matrix metalloproteinase-9.

circulation[23]. Radix Bupleuri targets the liver-gallbladder meridian, and when used together with *Platycodon grandiflorus* and Fructus Aurantii, it plays a synergistic role in soothing the liver and relieving depression[24]. Radix Rehmanniae and *Angelica sinensis* nourish the blood, regulate the qi flowing in the channels, and ensure the therapeutic effects of many drugs by preventing qi-regulating drugs from ascending, dispersing, and damaging yin and blood[25]. Licorice functions as a harmonizer of various drugs to ensure the full extent of curative effects[26]. All the above Chinese herbal medicines work synergistically to treat CHF complicated with depression, exerting a therapeutic effect by activating blood, removing blood stasis, and promoting qi circulation by removing blood stasis and stagnation. The results of TCM symptom scores showed that the research group scored significantly better than the control group in all seven symptoms (depression, frequent sighing, palpitations, fatigue, shortness of breath and weakness, pale complexion, and cold hands and feet) after treatment, indicating that XFZYD was significantly more effective in relieving symptoms in

patients with CHF complicated with depression compared with conventional Western medicine. Our evaluation of cardiac function revealed a notable reduction in LVEDD and LVESD in the research group after treatment, which were lower than the LVEDD and LVESD in the control group, whereas the LVEF was markedly elevated and higher in the research group compared with the control group, indicating that XFZYD has a positive mediating and stabilizing effect on cardiac function abnormalities in patients with CHF complicated with depression. Similar to our research results, Zhang *et al*[27], reported that XFZYD significantly shortened the duration of angina pectoris in patients with coronary heart disease, effectively improved their vascular endothelial function, and significantly reduced TCM symptom scores. Qi *et al*[28] confirmed that XFZYD showed higher efficacy than Western medicine for treating patients with various types of angina pectoris, which is related to the fact that the target network and cross-targets of XFZYD are closer to the target network of various types of angina compared with Western medicine. In terms of changes in depression, the research group exhibited greatly reduced SDS and HAMD scores after treatment, and these were lower than the pretreatment levels and those in the control group, suggesting that treatment with XFZYD in patients with CHF complicated with depression plays a prominent role in alleviating depression. Wang *et al*[29] reported that as a therapy for regulating qi and promoting blood circulation, XFZYD had a significant alleviating effect on depressive symptoms in patients with stable angina pectoris, which is consistent with our research results. Finally, the post-treatment levels of hs-CRP, MCP-1, and MMP-9 in the research group were significantly reduced and lower compared with those in the control group, indicating that XFZYD significantly inhibited serum inflammatory responses in patients with CHF complicated with depression, thereby hindering disease progression and playing an active therapeutic role.

CONCLUSION

In summary, XFZYD is superior to Western medicines such as flupentixol and melitracen in treating patients with CHF complicated with depression and exerts a significant therapeutic effect. Besides significantly relieving clinical TCM symptoms and enhancing cardiac function, this TCM therapy also relieves depression and markedly inhibits the levels of serum inflammatory factors. Our findings provide an optimized direction for the treatment of patients with CHF complicated with depression, as evidenced by changes in certain clinical values.

FOOTNOTES

Author contributions: Ying Wang designed the research and wrote the first manuscript; Ying Wang, Jun Wang, Wang Lv, Hu Chen, Qian Yang, Yang Zhang, Run Guo, Xiao-Li Ma and Qian-Yu Zhang contributed to conceiving the research and analyzing data; Ying Wang conducted the analysis and provided guidance for the research; all authors reviewed and approved the final manuscript.

Supported by Scientific Research Plan Project of Hebei Provincial Administration of Traditional Chinese Medicine, No. 2018507.

Institutional review board statement: This study was approved by the Ethic Committee of Cangzhou Central Hospital (Approval No. 2017-011-01).

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

Conflict-of-interest statement: Dr. Wang has nothing to disclose.

Data sharing statement: All data and materials are available from the corresponding author.

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S-Editor: Lin C

L-Editor: A

P-Editor: Zheng XM

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Retrospective Study

Effects of serum inflammatory factors, health index and disease activity scores on ankylosing spondylitis patients with sleep disorder

Hui Wang, Jia-Ying Sun, Yue Zhang

Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Wiatr M, Poland

Received: February 29, 2024

Revised: April 28, 2024

Accepted: May 22, 2024

Published online: June 19, 2024

Processing time: 111 Days and 4.3 Hours



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Abstract

BACKGROUND

Patients with ankylosing spondylitis (AS) frequently suffer from comorbid sleep disorders, exacerbating the burden of the disease and affecting their quality of life.

AIM

To investigate the clinical significance of serum inflammatory factors, health index and disease activity scores in patients with AS complicated by sleep disorders.

METHODS

A total of 106 AS patients with comorbid sleep disorders were included in the study. The patients were grouped into the desirable and undesirable prognosis groups in accordance with their clinical outcomes. The serum levels of inflammatory factors, including C-reactive protein, erythrocyte sedimentation rate, interleukin (IL)-6, tumour necrosis factor- α and IL-1 β , were measured. Disease activity scores, such as the Bath AS functional index, Bath AS disease activity index, Bath AS metrology index and AS disease activity score, were assessed. The health index was obtained through the Short Form-36 questionnaire.

RESULTS

The study found significant associations amongst serum inflammatory factors, health index and disease activity scores in AS patients with comorbid sleep disorders. Positive correlations were found between serum inflammatory factors and disease activity scores, indicating the influence of heightened systemic inflammation on disease severity and functional impairment. Conversely, negative correlations were found between disease activity scores and health index parameters, highlighting the effect of disease activity on various aspects of health-related quality of life. Logistic regression analysis further confirmed the predictive

value of these factors on patient outcomes, underscoring their potential utility in risk assessment and prognostication.

CONCLUSION

The findings demonstrate the intricate interplay amongst disease activity, systemic inflammation and patient-reported health outcomes in AS patients complicated by sleep disorders. The results emphasise the need for comprehensive care strategies that address the diverse needs and challenges faced by these patients and underscore the potential relevance of serum inflammatory factors, health index and disease activity scores as prognostic markers in this patient population.

Key Words: Inflammatory factors; Disease activity scores; Health index; Ankylosing spondylitis; Sleep disorders

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Core Tip: This study highlights the intricate associations between serum inflammatory factors, health index, and disease activity scores in ankylosing spondylitis (AS) patients with comorbid sleep disorders. Elevated serum inflammatory markers, including C-reactive protein, erythrocyte sedimentation rate, interleukin-6 (IL-6), tumor necrosis factor-alpha, and IL-1 β , are linked to increased disease activity, while the health index is negatively correlated with disease activity scores. These findings underscore the complexity of managing AS patients with concurrent sleep disturbances and emphasize the need for comprehensive care strategies that integrate systemic inflammation, disease activity, and patient-reported health outcomes.

Citation: Wang H, Sun JY, Zhang Y. Effects of serum inflammatory factors, health index and disease activity scores on ankylosing spondylitis patients with sleep disorder. *World J Psychiatry* 2024; 14(6): 866-875

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/866.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.866>

INTRODUCTION

Ankylosing spondylitis (AS) is a long-term inflammatory rheumatic condition marked by axial skeleton inflammation, frequently resulting in severe pain, rigidity and reduced functional ability[1,2]. It primarily affects the sacroiliac joints and the spine, resulting in structural and functional impairments that can significantly affect the quality of life of affected individuals[3]. Furthermore, AS is frequently associated with comorbidities, including sleep disorders, which can further exacerbate the burden of this disease[4-6]. Sleep disturbances in patients with AS have been attributed to various factors, including pain, discomfort and restricted physical mobility, leading to detrimental effects on physical and mental well-being[7,8].

The clinical management of AS has traditionally focused on alleviating inflammation, controlling symptoms and preserving physical functions[9,10]. However, the occurrence of sleep disorders in AS patients introduces an additional layer of complexity, because disrupted sleep patterns and quality can contribute to increased disease activity, augmented inflammatory responses and impaired health-related quality of life[10-13]. This multifaceted relationship emphasises the need to explore and delineate the clinical significance of serum inflammatory factors, health index and disease activity scores in AS patients with comorbid sleep disorders.

Serum inflammatory factors, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin (IL)-6, tumour necrosis factor-alpha (TNF- α) and IL-1 β , serve as key biomarkers of disease activity and inflammation in AS[14, 15]. Elevated levels of these inflammatory markers have been associated with increased disease severity, progression of structural damage and diminished functional capacity in AS patients[16]. Moreover, the presence of sleep disorders in AS may further potentiate the pro-inflammatory milieu, perpetuating a cycle of heightened disease activity and impaired well-being[17]. Thus, investigating the association between serum inflammatory factors and disease activity in AS patients with sleep disorders is pivotal for a comprehensive understanding of the disease pathophysiology and may offer insights into potential therapeutic targets to modulate the disease course.

In accordance with recent studies, key clinical tools, such as the Bath AS functional index (BASFI), Bath AS disease activity index (BASDAI), Bath AS metrology index (BASMI) and AS disease activity score (ASDAS), are crucial for assessing the overall disease burden and functional limitations in individuals with AS[18,19]. These composite indices reflect diverse aspects of disease activity, including pain, stiffness, fatigue, peripheral joint involvement and inflammatory markers, and thus, they offer a comprehensive representation of disease status. Understanding the correlations between serum inflammatory factors and disease activity scores in AS patients with sleep disorders can offer critical insights into the interplay amongst systemic inflammation, disease manifestations and patient-reported outcomes, guiding tailored therapeutic interventions and prognostication.

MATERIALS AND METHODS

A total of 106 AS patients with comorbid sleep disorders were admitted to the First Affiliated Hospital of Harbin Medical University from January 2022 to December 2023. The clinical data of these patients were retrospectively analysed. The study classified the patients into two prognosis groups: Desirable ($n = 52$) and undesirable ($n = 54$). This study was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University. The Ethics Committee has agreed to waive informed consent.

Inclusion and exclusion criteria

Inclusion criteria: (1) Subjects diagnosed with AS[20,21]; (2) patients with documented sleep disorders, including but not limited to obstructive sleep apnoea, insomnia, restless legs syndrome or other clinically diagnosed sleep disturbances [22]; and (3) availability of complete medical records.

Exclusion criteria: (1) Subjects with incomplete medical records; (2) patients with other chronic inflammatory conditions or systemic autoimmune diseases[23]; (3) patients with a history of significant psychiatric disorders, substance abuse or neurological conditions; (4) patients with recent acute infectious diseases or significant medical comorbidities; (5) patients currently receiving immunomodulatory or immunosuppressive therapies; and (6) pregnant or lactating women due to potential hormonal influences on the parameters under investigation[24].

Surgical procedures for AS

Surgical procedures for AS involve total hip arthroplasty *via* a lateral approach. The patient is positioned laterally with the affected side facing upwards, and the pelvic region is supported and immobilised using a body positioning frame at the pubic symphysis and sacrum. A posterior lateral curved incision, approximately 10 cm in length, is centred on the greater trochanter. An incision is then made layer by layer through the skin, *i.e.*, superficial fascia, exposing the iliotibial band and gluteus maximus. The iliotibial band and gluteus maximus are then incised, and the external rotators are exposed and cut at the insertion on the greater trochanter. The joint capsule is exposed and incised to dislocate the femoral head. The femoral neck is cut with a saw at the preoperatively determined and planned level on the lesser trochanter, and the femoral head is removed. The acetabulum is exposed, and the labrum and surrounding osteophytes are excised. The acetabulum is reamed to an appropriate depth, and the acetabular prosthesis and liner are implanted at an appropriate angle. The hip joint is flexed, adducted and internally rotated to expose the proximal femur, which is reamed to an appropriate size, and the femoral stem is implanted. An appropriate femoral head is selected, the joint is reduced and the stability of the joint is examined. The external rotator muscles are reconstructed, and the incision is closed layer by layer.

Observation indicators

BASDAI is a clinical assessment tool used to evaluate disease activity level in patients with AS[25]. It consists of 6 questions that assess fatigue, back pain, peripheral joint pain and swelling, enthesitis, severity of morning stiffness and duration. All items are evaluated using a 0-10 cm visual analogue scale, with 0 indicating no corresponding discomfort and 10 indicating extremely severe pain. When calculating the final score, the last 2 items are firstly added together and averaged, and then, the result is added to the sum of the previous 4 items and divided by 5.

BASFI is a tool used to assess the level of functional impairment in patients with AS[26]. It comprises 10 questions, and all items are assessed using a 0-10 cm visual analogue scale, and the final score is the average of the responses to the 10 questions. The calculation formula for ASDAS-D is as follows: $0.152 \times \text{back pain} + 0.069 \times \text{duration of morning stiffness} + 0.078 \times \text{fatigue} + 0.224 \times \text{sqrt (ESR)} + 0.400 \times \text{In (CRP} + 1)$. Here, back pain, duration of morning stiffness and fatigue correspond to the 2nd, 6th and 1st questions of BASDAI, respectively. 'Sqrt' denotes the square root, and 'In' denotes the natural logarithm. ESR is measured in mm/1 h by using the Westergren method, with normal values being ≤ 15 mm/1 h for males and ≤ 20 mm/1 h for females. CRP is tested using the immunoturbidimetric method, with normal values of ≤ 5 mg/L.

BASMI is a clinical tool used to assess the disease activity and level of functional impairment in AS[27]. It includes 5 items: Cervical flexion, lumbar side flexion, tragus-to-wall distance, thoracic expansion and fingertip-to-floor distance. Each item is scored in accordance with specific criteria, resulting in a comprehensive scoring system to assess a patient's spinal mobility and functional impairment. Each item is scored from 0 to 10, with higher scores indicating more severe disease.

ASDAS is an assessment tool for evaluating the disease activity of AS[28]. ASDAS-CRP combines CRP in its scoring, whilst ASDAS-ESR combines ESR in its scoring. Both scoring methods include considerations of morning stiffness, intensity of back pain, overall fatigue, chronic peripheral joint inflammatory disease activity and serum inflammatory biomarkers. Clinical assessments are conducted using a 10-point scale. For the 6 aforementioned components, a score of 0 indicates no symptoms, whilst the most severe score is 10. Morning stiffness that lasts 15 min scores 1 point, 2-4 h scores 4-6 points, 4-6 h scores 8 points and more than 6 h scores 10 points. $(\text{Duration of morning stiffness} + \text{severity of morning stiffness})/2 = \text{morning stiffness score}$.

The health index in this study was derived from the Short Form-36 questionnaire, a widely used tool for evaluating health status and quality of life. It includes 8 domains that encompass different aspects of health-related quality of life. Each domain is scored from 0 to 100 based on respondents' answers, with higher scores reflecting better health status for the respective domain. This questionnaire has been widely recognised for its comprehensive assessment of health-related quality of life[29].

Statistical analysis

The data were analysed using SPSS 25.0. Descriptive statistics for categorical data were presented as counts and percentages [n (%)]. For sample sizes ≥ 40 and theoretical frequencies $T \geq 5$, the chi-squared test was used with the basic formula, with the test statistic being χ^2 . If the sample size was ≥ 40 but the theoretical frequency was $1 \leq T < 5$, then the chi-squared test was adjusted using the correction formula. If the sample size was < 40 or the theoretical frequency was $T < 1$, then statistical analysis was conducted using Fisher's exact test. Normally distributed continuous data were expressed as the mean plus or minus the standard deviation (mean \pm SD). Non-normally distributed data were transformed to achieve normal distribution before conducting statistical analysis. For continuous data, the t -test was used, and Spearman's correlation analysis was employed for assessing correlations. Variables that presented statistically significant differences between the two groups were selected for binary logistic regression analysis.

RESULTS

The study compared the demographic characteristics, disease activity scores and health index of AS patients with sleep disorders (Table 1). A total of 106 patients were included, with 52 in the desirable prognosis group and 54 in the undesirable prognosis group. No statistically significant differences were found in age (44.13 ± 5.67 vs 45.28 ± 6.54 , $t = 0.962$, $P = 0.338$), sex distribution (male/female: 35/17 vs 38/16, $t = 0.017$, $P = 0.896$), disease duration (8.81 ± 2.34 vs 9.17 ± 3.12 , $t = 0.67$, $P = 0.504$), body mass index (26.45 ± 3.57 vs 27.89 ± 4.21 , $t = 1.897$, $P = 0.061$), smoking status (13.46% vs 20.37%, $t = 0.474$, $P = 0.491$), alcohol consumption (19.23% vs 25.93%, $t = 0.35$, $P = 0.554$), family history of cancer (23.08% vs 20.37%, $t = 0.01$, $P = 0.919$), hypertension (48.08% vs 38.89%, $t = 0.575$, $P = 0.448$), diabetes (26.92% vs 33.33%, $t = 0.257$, $P = 0.612$) and hyperlipidemia (44.23% vs 37.04%, $t = 0.309$, $P = 0.578$) between the two groups, indicating that the demographic characteristics were largely similar between the two groups. The above results indicate no statistically significant differences between the two groups, suggesting comparability and laying the foundation for subsequent research.

Sleep quality

The comparison of sleep quality parameters between the desirable and undesirable prognosis groups revealed no statistically significant differences (Table 2). In particular, the Pittsburgh sleep quality index (6.82 ± 1.68 vs 7.49 ± 1.98 , $t = 1.887$, $P = 0.062$), Epworth sleepiness scale (8.67 ± 1.42 vs 9.28 ± 2.15 , $t = 1.739$, $P = 0.085$), insomnia severity index (8.81 ± 2.03 vs 9.46 ± 3.19 , $t = 1.247$, $P = 0.216$), sleep efficiency ($85.46\% \pm 4.72\%$ vs $84.28\% \pm 5.64\%$, $t = 1.162$, $P = 0.248$) and total sleep time (6.89 ± 1.32 h vs 6.48 ± 1.14 h, $t = 1.729$, $P = 0.087$) did not demonstrate statistically significant differences between the two groups.

Inflammatory factors

The serum levels of inflammatory factors were compared between the desirable and undesirable prognosis groups in patients with AS complicated by sleep disorders (Table 3). The desirable prognosis group exhibited significantly lower CRP levels (6.17 ± 2.34 mg/L) compared with the undesirable prognosis group (7.52 ± 3.21 mg/L) ($t = 2.482$, $P = 0.015$). Similarly, ESR levels were significantly lower in the desirable prognosis group (16.56 ± 3.78 mm/h) compared with in the undesirable prognosis group (18.32 ± 4.91 mm/h) ($t = 2.076$, $P = 0.04$). TNF- α levels were also significantly lower in the desirable prognosis group (45.21 ± 9.33 pg/mL) compared with in the undesirable prognosis group (50.79 ± 12.54 pg/mL) ($t = 2.605$, $P = 0.011$). In addition, IL-6 Levels were significantly lower in the desirable prognosis group (28.14 ± 6.75 pg/mL) compared with in the undesirable prognosis group (32.79 ± 8.21 pg/mL) ($t = 3.195$, $P = 0.002$). Finally, IL-1 β levels were significantly lower in the desirable prognosis group (12.45 ± 3.88 pg/mL) compared with in the undesirable prognosis group (14.67 ± 4.21 pg/mL) ($t = 2.82$, $P = 0.006$). These findings suggest an association between lower serum inflammatory factor levels and improved prognosis in AS patients with comorbid sleep disorders.

Disease activity scores

Disease activity scores were compared between the desirable and undesirable prognosis groups in AS patients with sleep disorders, demonstrating significant differences (Table 4). The desirable prognosis group displayed lower scores across all parameters compared with the undesirable prognosis group. In particular, BASDAI scores were 3.21 ± 0.87 vs 4.67 ± 1.45 ($t = 6.304$, $P < 0.001$), BASFI scores were 2.98 ± 0.75 vs 3.72 ± 1.02 ($t = 4.267$, $P < 0.001$), BASMI scores were 2.34 ± 0.65 vs 3.78 ± 0.98 ($t = 8.957$, $P < 0.001$), ASDAS-CRP scores were 2.56 ± 0.68 vs 3.28 ± 1.21 ($t = 3.771$, $P < 0.001$) and ASDAS-ESR scores were 2.78 ± 0.72 vs 4.21 ± 1.14 ($t = 7.776$, $P < 0.001$). These results indicate that lower disease activity scores are associated with improved prognosis in AS patients with comorbid sleep disorders.

Health index

The health index parameters were compared between the desirable and undesirable prognosis groups in AS patients with sleep disorders, revealing notable differences (Table 5). Physical functioning scores were higher in the desirable prognosis group compared with in the undesirable prognosis group (62.78 ± 8.52 vs 58.92 ± 9.74 , $t = 2.175$, $P = 0.032$), as were the role-physical scores (48.73 ± 12.45 vs 43.62 ± 11.39 , $t = 2.203$, $P = 0.03$) and general health scores (60.94 ± 10.27 vs 56.33 ± 11.68 , $t = 2.161$, $P = 0.033$). Vitality scores were also higher in the desirable prognosis group compared with in the undesirable prognosis group (54.17 ± 7.94 vs 49.78 ± 9.63 , $t = 2.565$, $P = 0.012$). However, no significant difference was found in bodily pain scores (55.88 ± 9.76 vs 54.13 ± 8.92 , $t = 0.967$, $P = 0.336$). These findings suggest that higher health index scores, particularly in the domains of physical functioning, role-physical, general health and vitality, may be

Table 1 Demographic characteristics of ankylosing spondylitis patients with sleep disorders, *n* (%)

Parameters	Desirable prognosis group (<i>n</i> = 52)	Undesirable prognosis group (<i>n</i> = 54)	<i>t</i>	<i>P</i> value
Age (yr)	44.13 ± 5.67	45.28 ± 6.54	0.962	0.338
Sex (male/female)	35/17	38/16	0.017	0.896
Disease duration (yr)	8.81 ± 2.34	9.17 ± 3.12	0.67	0.504
Body mass index (kg/m ²)	26.45 ± 3.57	27.89 ± 4.21	1.897	0.061
Smoking status	7 (13.46)	11 (20.37)	0.474	0.491
Alcohol consumption	10 (19.23)	14 (25.93)	0.35	0.554
Family history of cancer	12 (23.08)	11 (20.37)	0.01	0.919
Hypertension	25 (48.08)	21 (38.89)	0.575	0.448
Diabetes	14 (26.92)	18 (33.33)	0.257	0.612
Hyperlipidemia	23 (44.23)	20 (37.04)	0.309	0.578

Table 2 Sleep quality in the desirable and undesirable prognosis groups

Parameters	Desirable prognosis group (<i>n</i> = 52)	Undesirable prognosis group (<i>n</i> = 54)	<i>t</i>	<i>P</i> value
Pittsburgh sleep quality index	6.82 ± 1.68	7.49 ± 1.98	1.887	0.062
Epworth sleepiness scale	8.67 ± 1.42	9.28 ± 2.15	1.739	0.085
Insomnia severity index	8.81 ± 2.03	9.46 ± 3.19	1.247	0.216
Sleep efficiency (%)	85.46 ± 4.72	84.28 ± 5.64	1.162	0.248
Total sleep time (h)	6.89 ± 1.32	6.48 ± 1.14	1.729	0.087

Table 3 Comparison of serum inflammatory factors between the desirable and undesirable prognosis groups

Parameters	Desirable prognosis group (<i>n</i> = 52)	Undesirable prognosis group (<i>n</i> = 54)	<i>t</i>	<i>P</i> value
CRP (mg/L)	6.17 ± 2.34	7.52 ± 3.21	2.482	0.015
ESR (mm/h)	16.56 ± 3.78	18.32 ± 4.91	2.076	0.04
TNF-α (pg/mL)	45.21 ± 9.33	50.79 ± 12.54	2.605	0.011
IL-6 (pg/mL)	28.14 ± 6.75	32.79 ± 8.21	3.195	0.002
IL-1β (pg/mL)	12.45 ± 3.88	14.67 ± 4.21	2.82	0.006

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TNF-α: Tumour necrosis factor-alpha; IL: Interleukin.

indicative of better prognosis in AS patients with comorbid sleep disorders, highlighting the clinical relevance of these parameters in assessing patient well-being and outcomes.

Correlation analysis

The correlation analysis revealed significant associations amongst serum inflammatory factors, health index and disease activity scores in patients with AS complicated by sleep disorders (Table 6). The serum levels of CRP, ESR, TNF-α, IL-6 and IL-1β exhibited positive correlations with disease activity scores (BASMI, BASDAI, ASDAS-CRP, BASFI and ASDAS-ESR), indicating a relationship between heightened inflammatory markers and increased disease activity. Conversely, the health index parameters (role-physical, general health, bodily pain, physical functioning and vitality) exhibited negative correlations with disease activity scores, suggesting that lower disease activity scores were associated with better health index outcomes. These findings underscore the interconnectedness of inflammatory factors, disease activity and health index in AS patients with comorbid sleep disorders, highlighting the clinical relevance of these associations in the management and prognosis of this patient population.

Logistic regression analysis

The logistic regression analysis demonstrated significant associations amongst serum inflammatory factors, health index and disease activity scores in patients with AS complicated by sleep disorders (Table 7). The serum levels of CRP, ESR,

Table 4 Comparison of disease activity scores between the desirable and undesirable prognosis groups

Parameters	Desirable prognosis group (n = 52)	Undesirable prognosis group (n = 54)	t	P value
BASDAI	3.21 ± 0.87	4.67 ± 1.45	6.304	P < 0.001
BASFI	2.98 ± 0.75	3.72 ± 1.02	4.267	P < 0.001
BASMI	2.34 ± 0.65	3.78 ± 0.98	8.957	P < 0.001
ASDAS-CRP	2.56 ± 0.68	3.28 ± 1.21	3.771	P < 0.001
ASDAS-ESR	2.78 ± 0.72	4.21 ± 1.14	7.776	P < 0.001

BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis metrology index; ASDAS: Ankylosing spondylitis disease activity score; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

Table 5 Health index in the desirable and undesirable prognosis groups

Parameters	Desirable prognosis group (n = 52)	Undesirable prognosis group (n = 54)	t	P value
Physical functioning	62.78 ± 8.52	58.92 ± 9.74	2.175	0.032
Role-physical	48.73 ± 12.45	43.62 ± 11.39	2.203	0.03
Bodily pain	55.88 ± 9.76	54.13 ± 8.92	0.967	0.336
General health	60.94 ± 10.27	56.33 ± 11.68	2.161	0.033
Vitality	54.17 ± 7.94	49.78 ± 9.63	2.565	0.012

Table 6 Correlation analysis of serum inflammatory factors, health index and disease activity scores in patients with as complicated by sleep disorders

Parameters	r	R ²	P value
CRP	0.235	0.055	0.015
ESR	0.199	0.039	0.041
TNF-α	0.246	0.061	0.011
IL-6	0.298	0.089	0.002
IL-1β	0.266	0.071	0.006
BASDAI	0.522	0.273	P < 0.001
BASFI	0.384	0.148	P < 0.001
BASMI	0.657	0.432	P < 0.001
ASDAS-CRP	0.344	0.118	P < 0.001
ASDAS-ESR	0.603	0.364	P < 0.001
Physical functioning	-0.208	0.043	0.032
Role-physical	-0.211	0.045	0.03
Bodily pain	-0.095	0.009	0.335
General health	-0.207	0.043	0.033
Vitality	-0.243	0.059	0.012

BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis metrology index; ASDAS: Ankylosing spondylitis disease activity score; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TNF-α: Tumour necrosis factor-alpha; IL: Interleukin.

Table 7 Logistic regression analysis of serum inflammatory factors, health index and disease activity scores in patients with ankylosing spondylitis complicated by sleep disorders

Parameters	Coefficient	Odds ratio	B	β	P value
CRP (mg/L)	0.174	1.19	2.353	0.174	0.019
ESR (mm/h)	0.094	1.098	1.999	0.094	0.046
TNF-α (pg/mL)	0.046	1.047	2.47	0.046	0.014
IL-6 (pg/mL)	0.084	1.087	2.938	0.084	0.003
IL-1β (pg/mL)	0.138	1.148	2.638	0.138	0.008
BASDAI	0.992	2.698	4.708	0.992	<i>P</i> < 0.001
BASFI	0.924	2.518	3.687	0.924	<i>P</i> < 0.001
BASMI	2.219	9.2	5.303	2.219	<i>P</i> < 0.001
ASDAS-CRP	0.749	2.115	3.343	0.749	<i>P</i> < 0.001
ASDAS-ESR	1.591	4.907	5.054	1.591	<i>P</i> < 0.001
Physical functioning	0.047	0.954	2.098	-0.047	0.036
Role-physical	0.037	0.964	2.132	-0.037	0.033
Bodily pain	0.021	0.98	0.969	-0.021	0.333
General health	0.038	0.962	2.093	-0.038	0.036
Vitality	0.057	0.945	2.441	-0.057	0.015

BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis metrology index; ASDAS: Ankylosing spondylitis disease activity score; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TNF-α: Tumour necrosis factor-alpha; IL: Interleukin.

TNF-α, IL-6 and IL-1β, and the disease activity scores (BASDAI, BASFI, BASMI, ASDAS-CRP and ASDAS-ESR), were found to have positive coefficients and odds ratios, signifying their potential predictive value in the presence of the outcome of interest. Conversely, the health index parameters (physical functioning, role-physical, bodily pain, general health and vitality) exhibited negative coefficients and odds ratios, suggesting their roles in predicting positive outcomes in this patient population. These findings emphasise the predictive significance of these factors in patient outcomes, underscoring their utility in informing clinical decision-making and patient management strategies in AS patients with comorbid sleep disorders.

DISCUSSION

This study aimed to find associations amongst serum inflammatory factors, health index and disease activity scores in patients with AS and comorbid sleep disorders. Notably, the findings revealed significant correlations amongst these parameters, indicating a complex interrelation amongst disease activity, systemic inflammation and patient-reported health status. The positive correlations of the serum levels of CRP, ESR, TNF-α, IL-6 and IL-1β with disease activity scores (BASDAI, BASFI, BASMI and ASDAS) highlight the influence of heightened systemic inflammation on disease severity and functional impairment in AS patients with sleep disorders. These findings are aligned with previous research that demonstrates the central role of inflammatory markers in driving disease activity and structural damage in AS. Eichberger *et al*[30] also confirmed a similar effect[30]. In addition, the present study extends this understanding by elucidating the relevance of serum inflammatory factors in the context of comorbid sleep disorders, implicating their potential contribution to the multifaceted burden experienced by these patients.

Moreover, this study demonstrated negative correlations between disease activity scores and health index parameters, particularly in domains related to physical functioning, role-physical, general health and vitality. Kaneko *et al*[31] mentioned similar viewpoints[31]. The current study highlights the effect of disease activity on various aspects of health-related quality of life, underscoring the pervasive influence of AS and sleep disorders on patient well-being. The findings are aligned with the multifactorial nature of AS, where disease activity encompasses not only physical symptoms but also exerts profound effects on emotional and social functioning, vitality and overall health perception. Moreover, the findings of the study underscore the integrated nature of disease activity and health-related quality of life, emphasising the need for comprehensive patient care that addresses inflammatory disease manifestations and their effect on various dimensions of patient-reported outcomes.

Furthermore, logistic regression analysis provided insights into the predictive value of serum inflammatory factors, health index and disease activity scores in AS patients with comorbid sleep disorders. The positive coefficients and odds

ratios associated with serum inflammatory factors and disease activity scores signify their potential as predictive markers for adverse outcomes in this patient population, reflecting their utility in prognostication and risk stratification. Similar findings were reported by Sigmund *et al*[32]. Conversely, the negative coefficients and odds ratios observed for health index parameters imply their role as predictors of favourable outcomes, highlighting their importance in identifying patients with better health-related quality of life and functional status. These findings hold clinical significance, offering valuable insights for the risk assessment, treatment planning and monitoring of AS patients with concurrent sleep disorders.

This study also compared demographic characteristics, sleep quality, serum inflammatory factors, health index and disease activity scores between the desirable and undesirable prognosis groups in AS patients with sleep disorders. The analysis revealed no statistically significant differences in demographic characteristics and sleep quality parameters between the two groups, underscoring the relevance of serum inflammatory factors, health index and disease activity scores as potential determinants of prognosis in this patient population. Moreover, the study findings contribute to the understanding of prognostic factors in AS patients with comorbid sleep disorders, emphasising the need for tailored approaches that address the complex interplay of disease activity, systemic inflammation and patient-reported outcomes in clinical decision-making.

Overall, the study findings illuminate the intricate associations amongst serum inflammatory factors, health index and disease activity scores in AS patients complicated by sleep disorders, providing valuable insights into the multifaceted burden experienced by this patient population. These findings have significant clinical implications, emphasising the need for holistic approaches that integrate the assessment of systemic inflammation, disease activity and patient-reported health outcomes in the management of AS patients with concurrent sleep disorders. The multifaceted nature of AS, compounded by the presence of sleep disturbances, underscores the importance of comprehensive care strategies that extend beyond traditional disease-modifying therapies to address the diverse needs and challenges faced by these patients.

The study findings also underscore the potential relevance of serum inflammatory factors, health index and disease activity scores as prognostic markers in AS patients with comorbid sleep disorders, offering valuable insights for risk assessment and patient stratification. These findings complement existing knowledge on the pathophysiology and clinical manifestations of AS, shedding light on the complexities of managing a chronic inflammatory rheumatic disease in the context of sleep disturbances. Furthermore, the findings highlight the need for multidisciplinary care models that encompass rheumatological, sleep medicine and psychological support to optimise patient outcomes and well-being.

Despite the contributions of this study, several limitations should be acknowledged. The findings may have limited generalisability due to the retrospective design and relatively small sample size. In addition, the study did not explore specific interventions that target sleep disorders or systemic inflammation, warranting further research to elucidate the potential effects of targeted therapies on disease activity and health outcomes in this patient population. Future prospective studies with larger cohorts and longitudinal follow-up are warranted to validate the findings and explore the longitudinal associations amongst serum inflammatory factors, health index and disease activity scores in AS patients with sleep disorders.

In consideration of our study's implications for clinical decision-making and patient care, underscoring the role of incorporating the comprehensive assessments of sleep quality and inflammatory status into the routine clinical evaluation of AS patients is imperative. Our findings underscore the importance of a multidimensional approach to patient care, emphasising the need for rheumatologists and healthcare providers to consider the bidirectional relationships amongst AS, systemic inflammation and sleep disturbances when formulating tailored treatment strategies. Furthermore, the integration of validated patient-reported outcome measures that assess sleep patterns and perceived sleep quality can offer valuable insights into disease management and treatment response, informing the development of personalised care plans for AS patients with concurrent sleep disorders.

We recognise the importance of confirming and expanding upon the current results through prospective, larger-scale studies to establish the robustness and generalisability of our findings. Future research endeavours will involve the implementation of prospective cohort studies with larger patient populations to validate the associations amongst serum inflammatory factors, health index and disease activity scores in AS patients complicated by sleep disorders. By increasing sample size and employing a longitudinal approach, these studies will provide a comprehensive understanding of the longitudinal associations and predictive value of these parameters in informing clinical decision-making and patient management strategies. In particular, the incorporation of longitudinal follow-up will enable the assessment of the temporal relationships amongst serum inflammatory factors, disease activity and patient-reported health outcomes, shedding light onto the dynamic nature of these interrelations over time.

CONCLUSION

In conclusion, the present study provides valuable insights into the clinical significance of serum inflammatory factors, health index and disease activity scores in patients with AS complicated by sleep disorders. The findings underscore the intricate interplay amongst systemic inflammation, disease activity and patient-reported health outcomes in this patient population, highlighting the multifaceted burden experienced by AS patients with concurrent sleep disturbances. These findings hold implications for tailored therapeutic interventions, risk assessment and patient stratification, emphasising the importance of a comprehensive approach to address the diverse needs and challenges faced by these patients.

ACKNOWLEDGEMENTS

I would like to express my gratitude to all those who helped me during the writing of this thesis. I acknowledge the help of my colleagues, Jian-Yang Zhuang, who gave me advice on academic research.

FOOTNOTES

Author contributions: Wang H and Zhang Y initiated the project, designed the experiment and conducted clinical data collection; Sun JY performed postoperative follow-up and recorded data; Wang H and Zhang Y conducted collation and statistical analyses and wrote the original manuscript; All the authors read and approved the final manuscript.

Supported by the Immuno Inflammatory Diseases Research Support Project, No. J202301E036.

Institutional review board statement: This study was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University.

Informed consent statement: The Ethics Committee has agreed to waive informed consent.

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

Data sharing statement: All data generated or analysed during this study are included in this published article.

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S-Editor: Li L

L-Editor: A

P-Editor: Chen YX

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Retrospective Study

Personalized and continuous care intervention affects rehabilitation, living quality, and negative emotions of patients with breast cancer

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Kandasamy R

Received: February 29, 2024

Revised: April 22, 2024

Accepted: April 25, 2024

Published online: June 19, 2024

Processing time: 111 Days and 4.1 Hours



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Abstract

BACKGROUND

Breast cancer is among the most common malignancies worldwide. With progress in treatment methods and levels, the overall survival period has been prolonged, and the demand for quality care has increased.

AIM

To investigate the effect of individualized and continuous care intervention in patients with breast cancer.

METHODS

Two hundred patients with breast cancer who received systemic therapy at The First Affiliated Hospital of Hebei North University (January 2021 to July 2023) were retrospectively selected as research participants. Among them, 134 received routine care intervention (routing group) and 66 received personalized and continuous care (intervention group). Self-rating anxiety scale (SAS), self-rating depression scale (SDS), and Functional Assessment of Cancer Therapy-Breast (FACT-B) scores, including limb shoulder joint activity, complication rate, and care satisfaction, were compared between both groups after care.

RESULTS

SAS and SDS scores were lower in the intervention group than in the routing group at one and three months after care. The total FACT-B scores and five dimensions in the intervention group were higher than those in the routing group at three months of care. The range of motion of shoulder anteflexion, posterior extension, abduction, internal rotation, and external rotation in the intervention group was higher than that in the routing group one month after care. The incidence of postoperative complications was 18.18% lower in the intervention

group than in the routing group (34.33%; $P < 0.05$). Satisfaction with care was 90.91% higher in the intervention group than in the routing group (78.36%; $P < 0.05$).

CONCLUSION

Personalized and continuous care can alleviate negative emotions in patients with breast cancer, quicken rehabilitation of limb function, decrease the incidence of complications, and improve living quality and care satisfaction.

Key Words: Breast cancer; Personalized care; Continuous care; Negative emotions; Living quality; Rehabilitation effect

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Core Tip: Surgery is currently the treatment of choice for breast cancer. Long-term rehabilitation exercises are necessary after surgery due to surgical trauma. At the same time, surgery alters breast structure, increases the patient's psychological stress response, and makes them prone to negative emotions, affecting quality of life and adherence to recovery. Therefore, there is a need to find a care model that improves the negative emotions and quality of life of patients and promotes their recovery.

Citation: Kong LX, Zhao YH, Feng ZL, Liu TT. Personalized and continuous care intervention affects rehabilitation, living quality, and negative emotions of patients with breast cancer. *World J Psychiatry* 2024; 14(6): 876-883

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/876.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.876>

INTRODUCTION

According to 2020 data from the International Cancer Research Center, there are approximately 2.3 million new cases of breast cancer, making it the most common cancer in the world[1]. Currently, breast cancer therapy is mostly based on surgery supplemented with radiotherapy and chemotherapy[2]. Long-term treatment remains a significant challenge for patients with breast cancer. They not only suffer from physical pain, including fatigue, lack of physical function, and side effects of treatment, but also bear a variety of psychological pressures, such as uncertainty in disease prognosis, lack of family role function, and economic burden, which often lead to negative emotions, decreased quality of life, and serious adverse effects on rehabilitation[3,4]. The key issue in clinical nursing is alleviating negative emotions in patients with breast cancer, improving their quality of life, and encouraging them to gradually return to society. In recent years, personalized and continuous care has received increasing attention in the field of oncology. Personalized care is patient-centered, focuses on meeting the individual needs of patients, and provides better services[5]. Continuous care provides patients with medical, nursing, and rehabilitation guidance services after discharge, which is conducive to them receiving reliable and complete rehabilitation guidance[6]. Therefore, this study applied personalized and continuous care to the management of breast cancer and aims to serve as a reference for nursing work.

MATERIALS AND METHODS

Patient characteristics

Two hundred patients with breast cancer who received systemic therapy at The First Affiliated Hospital of Hebei North University from January 2021 to July 2023 were retrospectively selected as research participants. The inclusion criteria were as follows: (1) Pathological examination that diagnosed breast cancer for the first time; (2) female patients; (3) patients aged between 30 and 60 years; (4) a treatment plan that included surgery combined with chemotherapy and radiotherapy; and (5) routine or personalized and continuous care received during treatment. The exclusion criteria were as follows: (1) Suffering from heart, brain, liver, or other major organ diseases; (2) combination of malignant tumors and immune, blood system, and infectious diseases; (3) observed mental and cognitive disorders; (4) patients with a previous history of chest surgery; (5) patient loss for follow-up and to death; (6) pregnant or lactating women; and (7) incomplete clinical data.

Care intervention methods

The routing group received routine care, including condition monitoring, health education, and follow-up, as well as medication, psychological, perioperative, and rehabilitation care, and so on. The intervention group received individualized and continuous care based on the routine care. This involved the following: (1) Establishment of a care group composed of head nurses and multiple nursing staff. After admission, the patient's condition and family situation were recorded in a case file through data collection. The group collectively evaluated the patient's condition and potential risk factors and then developed a personalized care plan in line with the actual situation through discussions; (2) Health education and psychological care: Combined with the patient's cultural level, knowledge of health education on breast

cancer surgery, perioperative precautions, and possible adverse reactions after surgery were provided through oral presentations, handbooks, videos, and other means to deepen their understanding. The psychological changes in patients were closely observed, care given when considering speech and physical behavior, and questions regarding any of their doubts were answered patiently. Targeted psychological education should be carried out by psychologists when necessary; (3) Life care: Encouraged patients to express their inner needs and strove to create a comfortable sickroom environment. Based on the patient's personal preferences and overall condition, personalized recipes were developed to ensure nutritional intake; (4) Perioperative care: Postoperative changes in patients were closely monitored to ensure early treatment of complications. After the patient's postoperative condition stabilized, the responsible nurse provided one-on-one functional exercise guidance, and the exercise intensity was based on the patient's tolerance. After the patients and their families mastered the exercise methods, the exercise situation was registered daily to provide continuous and periodic functional exercise guidance; and (5) Out-hospital care: Through the "intelligent health education system" to achieve continuous care for patients, the nursing staff dynamically tracked the patient's condition after discharge on the platform and used a questionnaire survey to grasp information on the medication, diet, and exercise in detail. According to feedback information from the platform, the nursing team developed a new management plan for patients every two weeks and set up a punch card to urge them to implement it.

Index measurements

Negative emotions: Before and one and three months after care, the self-rating anxiety scale (SAS) and the self-rating depression scale (SDS)[7] were used to assess the negative emotions of patients. Both the SAS and SDS include 20 items, each of which can be rated on a scale of 1-4, with a total score of 20-80. The SAS is bounded by 50 scores: 50-59, mild anxiety; 60-69, moderate anxiety; and >69, severe anxiety. The SDS is bounded by 53 scores: 53-62, mild depression; 63-72, moderate depression; and 72, severe depression. In this study, the total score of the two scales multiplied by 1.25 was converted into a percentage system to present its integer part, with a final full score of 100 points.

Living quality: Before and three months after care, the Functional Assessment of Cancer Therapy-Breast (FACT-B)[8] was used to assess the quality of life of patients. FACT-B includes five subscales and 36 items, namely, physiological (seven items), emotional (six items), social (seven items), and functional well-being (seven items), as well as a specific breast cancer subscale (nine items). Each item can be rated on a scale of 0-4, with a total score ranging from 0-144. A higher score indicates a better living quality.

Limb shoulder joint activity: Before and one month after care, the angles of shoulder anteflexion, posterior extension, abduction, internal rotation, and external rotation were measured using a protractor.

Complications: Postoperative complications in the two patient groups were compared, such as flap necrosis, upper limb lymphedema, wound infection, and subcutaneous effusion.

Care satisfaction: A self-made care satisfaction questionnaire was used to assess patient satisfaction with nursing work. There are 20 items in the questionnaire, each of which can be rated on a scale of 1-5, with a total score of 20-100. A total questionnaire score of ≤ 59 indicates unsatisfied, between 60 and 89 indicates satisfied, and ≥ 90 indicates greatly satisfied. Care satisfaction = (satisfied + greatly satisfied) / total number of cases.

Statistical analysis

SPSS 26.0n software was used for all data analyses. Quantitative data according to abnormal distribution were shown as the mean \pm SD. A paired sample *t*-test was adopted for intragroup comparison, and an independent sample *t*-test for intergroup comparison. Qualitative data are shown as cases and percentages [*n* (%)], which were compared using the chi-square and Fisher's exact tests when more than 20% of the theoretical frequency was < 5 , or when the theoretical frequency was < 1 . Repeated measures analysis of variance was used to compare the data at different times between groups, which was then corrected using a Bonferroni test. Statistical significance was set at $P < 0.05$.

RESULTS

General data

In total, 134 patients who received routine care were included in the routing group, and 66 patients who received personalized and continuous care included in the intervention group. There were no statistically significant differences in the general data between the two groups ($P > 0.05$; Table 1).

Negative emotions

One month after care, the SAS total scores of the routing and intervention groups were 63.06 ± 8.02 and 60.64 ± 7.20 , respectively. Three months after care, the SAS total scores of the routing and intervention groups were 57.44 ± 4.70 and 55.70 ± 5.19 , respectively. The SAS scores in the intervention group were lower than those in the routing group at one and three months after care ($P < 0.05$; Figure 1A). Results of the repeated measures analysis of variance showed that the major effect of the number of measurements was significant ($F = 98.041$, $P < 0.001$), whereas the major effect of the group and the interaction effect were not ($F = 3.341/2.808$, $P = 0.069/0.066$).

Table 1 Comparison of the general data between the routing and intervention groups

Data	Routing group (n = 134)	Intervention group (n = 66)	<i>t/χ²/Z</i>	<i>P</i> value
Age (yr, mean ± SD)	43.75 ± 7.15	45.39 ± 4.67	1.954	0.052
BMI (kg/m ² , mean ± SD)	23.40 ± 1.23	23.59 ± 1.84	0.747	0.457
Marital status [<i>n</i> (%)]			0.186	0.918
Spinsterhood	7 (5.22)	4 (6.06)		
Married	106 (79.11)	53 (80.30)		
Divorced/widowed	21 (15.67)	9 (13.64)		
Cultural levels [<i>n</i> (%)]			0.154	0.878
Junior school or below	25 (18.66)	11 (16.67)		
High school/technical secondary school	76 (56.72)	39 (59.09)		
College or higher	33 (24.62)	16 (24.24)		
Sources of treatment costs [<i>n</i> (%)]			3.890	0.149
Fee	22 (16.42)	8 (12.12)		
Medical insurance	96 (71.64)	55 (83.33)		
Private expense	16 (11.94)	3 (4.55)		
Tumor diameter (cm, mean ± SD)	4.16 ± 1.05	4.41 ± 0.98	1.623	0.104
Lesion localization [<i>n</i> (%)]			1.232	0.550
Left side	62 (46.27)	29 (43.94)		
Right side	58 (43.28)	32 (48.48)		
Both sides	14 (10.45)	5 (7.58)		
TNM [<i>n</i> (%)]			1.763	0.078
I	29 (21.64)	9 (13.64)		
II	82 (61.19)	40 (60.61)		
III	23 (17.16)	17 (25.76)		
Pathological type [<i>n</i> (%)]			1.140	0.802
Early invasive cancer	12 (8.96)	5 (7.58)		
Invasive nonspecific carcinoma	110 (82.09)	58 (87.88)		
Specific invasive carcinoma	7 (5.22)	2 (3.03)		
Else	5 (3.73)	1 (1.52)		
Operation mode [<i>n</i> (%)]			0.178	0.724
Mastectomy surgery	102 (98.51)	52 (78.79)		
Breast conservation	32 (23.88)	14 (21.21)		

BMI: Body mass index; TNM: Tumor node metastasis.

One month after care, the SDS total scores of the routing and intervention groups were 58.45 ± 5.35 and 56.02 ± 5.85 , respectively. Three months after care, the SDS total scores of the routing and interventions groups were 55.96 ± 4.71 and 53.33 ± 4.12 , respectively. The SDS scores in the intervention group were lower than those in the routing group at one and three months after care ($P < 0.05$; **Figure 1B**). Results of repeated measures analysis of variance showed that the major effects of the group and number of measurements were significant ($F = 18.406/93.001$, $P < 0.001$), and there was no interaction effect between the grouping and number of measurements ($F = 0.185$, $P = 0.831$).

Living quality

Three months after care, total FACT-B scores and its five dimensions in both patient groups were greater than those before care intervention, where those recorded for the intervention group were higher than those in the routing group (**Table 2**).

Table 2 Comparison of the Functional Assessment of Cancer Therapy-Breast scores between the routing and intervention groups (points, mean ± SD)

Time	Group	Case	Physiological well-being	Emotional well-being	Social well-being	Functional well-being	Specific breast cancer subscale	Total points
T ₁	Routing group	134	18.45 ± 3.39	16.09 ± 2.67	17.10 ± 3.64	15.06 ± 4.05	19.96 ± 4.35	86.65 ± 8.05
	Intervention group	66	17.82 ± 4.51	16.67 ± 3.55	17.53 ± 4.07	15.77 ± 2.47	21.08 ± 4.92	88.68 ± 8.46
	<i>t</i> value		1.002	1.169	0.761	1.538	1.639	1.799
	<i>P</i> value		0.630	0.245	0.447	0.126	0.103	0.074
T ₂	Routing group	134	20.50 ± 3.34 ^a	18.60 ± 3.42 ^a	22.08 ± 3.13 ^a	19.37 ± 3.45 ^a	23.71 ± 3.33 ^a	104.27 ± 7.87 ^a
	Intervention group	66	22.27 ± 2.80 ^a	20.56 ± 1.72 ^a	23.68 ± 2.75 ^a	22.61 ± 2.40 ^a	26.29 ± 2.18 ^a	115.41 ± 5.85 ^a
	<i>t</i> value		3.940	5.382	3.532	7.697	6.556	11.249
	<i>P</i> value		< 0.001	< 0.001	0.001	< 0.001	< 0.001	< 0.001

^a*P* < 0.05, comparison of the same group before care.
T₁: Before care intervention; T₂: After three months of care intervention.

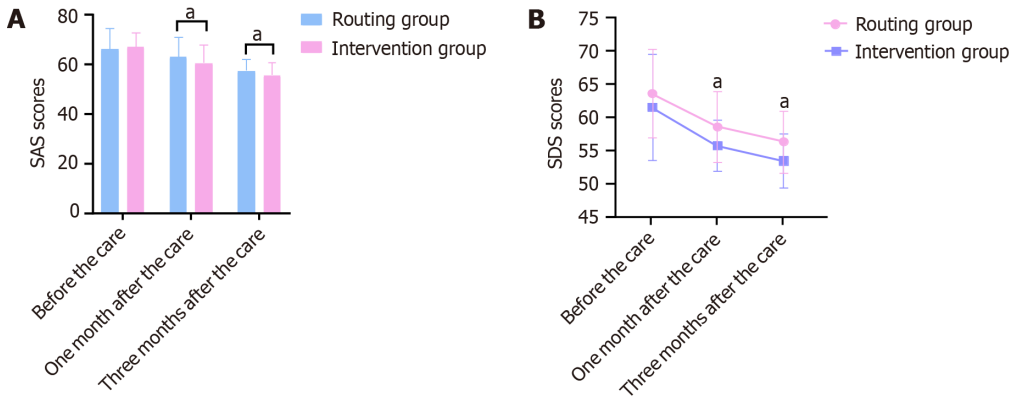


Figure 1 Comparison of the self-rating anxiety scale and self-rating depression scale scores between the routing and intervention groups. A: Self-rating anxiety scale scores; B: Self-rating depression scale scores. SAS: Self-rating anxiety scale; SDS: Self-rating depression scale. ^a*P* < 0.05.

Limb shoulder joint activity

One month after care, the range of motion of shoulder anteflexion, posterior extension, abduction, internal rotation, and external rotation in both groups was lower than that before care intervention, where that recorded in the intervention group was higher than that in the routing group (*P* < 0.05; Table 3).

Complications

The incidence of postoperative complications was 34.33% (46/134) and 18.18% (12/66) in the routing and intervention groups, respectively, with the intervention group showing the lowest incidence than the routing group (*P* < 0.05; Table 4).

Care satisfaction

Care satisfaction of the routing group was 78.36% (105/134) and that of the intervention group 90.91% (60/66). Thus, patients in the intervention group noted higher care satisfaction than those in the routing group (*P* < 0.05; Table 5).

Table 3 Comparison of limb shoulder joint activity of the affected limb between the routing and the intervention groups (°, mean ± SD)

Time	Group	Case	Anteflexion	Posterior extension	Abduction	Internal rotation	External rotation
T ₁	Routing group	134	150.39 ± 11.57	40.75 ± 3.25	161.97 ± 8.14	72.10 ± 5.63	77.26 ± 5.72
	Intervention group	66	148.97 ± 13.99	39.68 ± 5.24	163.03 ± 7.21	73.97 ± 7.67	75.70 ± 6.69
	<i>t</i> value		0.760	1.514	0.899	1.763	1.629
	<i>P</i> value		0.448	0.134	0.370	0.081	0.106
T ₂	Routing group	134	123.90 ± 14.14 ^a	28.49 ± 4.58 ^a	115.48 ± 7.37 ^a	60.00 ± 8.66 ^a	64.37 ± 5.29 ^a
	Intervention group	66	130.97 ± 17.07 ^a	32.83 ± 5.59 ^a	126.21 ± 9.40 ^a	64.65 ± 9.34 ^a	67.58 ± 8.44 ^a
	<i>t</i> value		3.102	5.470	8.131	3.481	2.822
	<i>P</i> value		0.002	< 0.001	< 0.001	0.001	0.006

^a*P* < 0.05, comparison of the same group before care.

T₁: Before care intervention; T₂: After one month of care intervention.

Table 4 Comparison of complications between the routing and intervention groups, *n* (%)

Group	Case	Skin flap necrosis	Upper limb lymphadenoma	Scalp hydrops	Wound infection	Else	Total
Routing group	134	7 (5.22)	17 (12.69)	4 (2.99)	12 (8.96)	6 (4.48)	46 (34.33)
Intervention group	66	2 (3.03)	6 (9.09)	0	3 (4.55)	1 (1.52)	12 (18.18)
χ^2							5.075
<i>P</i> value							0.024

Table 5 Comparison of care satisfaction between the routing and intervention groups, *n* (%)

Group	Case	Not satisfied	Satisfied	Very satisfied	Total
Routing group	134	29 (21.64)	69 (51.49)	36 (26.87)	105 (78.36)
Intervention group	66	6 (9.09)	34 (51.52)	26 (39.39)	60 (90.91)
χ^2					4.825
<i>P</i> value					0.028

DISCUSSION

Breast cancer results from a change in the biology of cancer cells in the epicenter of the breast gland owing to the role of multiple carcinogens, resulting in massive numbers of infantile cancer cells proliferating endlessly, crowding and destroying normal cellular organization, and damaging the structure of the breast[9,10]. The breast is not an organ that maintains vital motion in humans. However, because breast gland cells forfeit the specificity of normocytes, the connections between tissues are loose and easily detached. Once cancer cells are shed, they can spread throughout the body *via* the blood or lymph, resulting in potentially life-threatening metastases[11].

The main principles of clinical treatment for breast cancer are early discovery, diagnosis, and therapy. At present, for most of the clinical procedures used in breast cancer radical surgery to further improve efficacy, the application of chemotherapy, radiotherapy, and other adjuvant therapies is critical[12]. With the continuous increase in treatment methods and levels, the survival rate of patients with breast cancer has increased, but the disease itself and treatment measures still cause unavoidable adverse effects in patients[13]. Statistically, patients with breast cancer have five- and ten-year survival rates of approximately 90% and 80%, respectively[14]. Therefore, improving a patient's quality of life has become a key concern. Patients with breast cancer are prone to negative emotions during diagnosis and treatment. In a study of 2235 patients with breast cancer, 48.6% and 15% of them reported varying levels of anxiety and depression, respectively[15]. These emotions can seriously influence therapeutic effects and quality of life, increasing the risk of breast cancer recurrence and metastasis, shortening survival time, and increasing cancer mortality[16,17].

Routine care only attaches importance to the patient's condition and physical state, lacks targeted nursing measures to improve negative emotions and living quality, and the contract between the patient and the hospital ends after discharge; more services are provided to the patient through telephone follow-up and by other means, which make it difficult to effectively meet the needs of the patient[18]. Personalized care is based on scientific and humanized concepts. It generally requires doctors, patients, and family members to participate in the entire nursing process, including personalized evaluation, nursing plan formulation, efficient implementation, other aspects of nursing measures, is patient-centered, and requires improved nursing efficiency and quality[19]. Continuous care extends inpatient care services to families or communities to meet the health needs of discharged patients. It is an important nursing measure to accelerate the early rehabilitation of patients and is an indispensable part of deepening high-quality nursing[20].

In this study, personalized and continuous care was used for patients with breast cancer, and the results were as follows: (1) One and three months after care, the SAS and SDS scores in the intervention group were lower than those in the routing group; (2) Three months after care, the total FACT-B scores and the five associated dimensions in the intervention group were greater than those in the routing group; (3) One month after care, the range of motion of shoulder anteflexion, posterior extension, abduction, internal rotation, and external rotation in the intervention group was higher than that in the routing group; (4) Complications in the intervention group were less than those observed in the routing group; and (5) Care satisfaction of the intervention group was higher than that of the routing group. The reason is that, according to the theory of personalized and continuous care, nursing staff can provide targeted psychological counseling and catharsis; they can also develop appropriate cognitive intervention measures based on the patient's cultural level and acceptance. This helps to correct misconceptions and effectively reduce negative emotions. After breast cancer surgery, lifting the upper limb becomes challenging due to the need to remove the pectoralis major muscle and nerve. Additionally, dissection of axillary lymph nodes can block lymphatic reflux, leading to upper limb edema. Therefore, postoperative upper limb functional exercises are crucial for reducing scar traction and restoring limb function. After surgery, patients undergo guided early functional exercises with personalized plans tailored to their capabilities in terms of intensity, frequency, and duration. Following discharge, an online platform promptly provides patients with health-related information to address any difficulties. This enables patients to actively cooperate with treatment, while significantly reducing postoperative complications, promoting limb function recovery, and improving quality of life. Furthermore, personalized and continuous care focuses on establishing a strong ongoing connection with patients, while prioritizing their feelings and needs throughout the nursing process to improve acceptance and satisfaction.

There are some limitations to this study. Briefly, the number of samples included in this study was small and only used data from a single center. Therefore, the study conclusions need to be confirmed through future randomized controlled trials with larger sample sizes and involve multiple centers.

CONCLUSION

In summary, the application of personalized and continuous care in breast cancer therapy has a significant effect on alleviating negative emotions, accelerating the rehabilitation of limb function, decreasing the incidence of postoperative complications, and improving quality of life and care satisfaction. Overall, these findings are worthy of further extension and application.

FOOTNOTES

Author contributions: Kong LX designed the research and wrote the paper; Zhao YH analyzed the data and reviewed the paper; Feng ZL and Liu TT collected the information and revised the paper; all authors have read and approve the final manuscript.

Supported by Zhangjiakou Science and Technology Plan Project, No. 2322112D.

Institutional review board statement: This study was reviewed and approved by the Institutional Ethics Committee of The First Affiliated Hospital of Hebei North University.

Informed consent statement: The Institutional Ethics Committee approved an exemption from informed consent.

Conflict-of-interest statement: Dr. Kong has nothing to disclose.

Data sharing statement: The data used in this study can be obtained from the corresponding author upon request.

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0009-0002-8311-710X.

S-Editor: Lin C

L-Editor: A

P-Editor: Che XX

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Retrospective Study

Computerized cognitive remediation therapy on cognitive impairment and social function in patients with chronic schizophrenia

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Simos P, Netherlands

Received: March 4, 2024

Revised: April 28, 2024

Accepted: May 20, 2024

Published online: June 19, 2024

Processing time: 107 Days and 4.9 Hours



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Abstract

BACKGROUND

Patients with schizophrenia may have various disease manifestations, most of which gradually tend toward incurable chronic decline, leading to mental disability. The basic symptoms of the disease can impair social function, whereas long-term hospitalization produces hospitalization syndrome, causing serious damage to social function.

AIM

To investigate the effects of Computerized Cognitive Remediation Therapy (CCRT) on cognitive and social functioning in patients with chronic schizophrenia.

METHODS

A retrospective analysis of 120 patients with chronic schizophrenia in Shanghai Pudong New Area Mental Health Center was performed. They were divided into an intervention group (60 cases treated with CCRT combined with conventional medication) and a control group (60 cases treated with conventional medication). After treatment, effects on cognitive function and social roles were observed in both groups. The Positive and Negative Syndrome Scale (PANSS) was used to assess the patients' psychiatric symptoms. The Wisconsin Card Sorting Test (WCST) was used to assess the patients' cognitive functioning, and the Social Functioning Scale for Psychiatric Inpatients (SSPI) was used to assess the social functioning of the inpatient psychiatric patients.

RESULTS

No significant differences were observed in the PANSS, WCST, and SSPI intergroup scores before treatment ($P > 0.05$). After 2, 4, and 6 wk of therapy, general psychopathological factors, positive symptoms, negative symptoms, and total PANSS scores of PANSS in the intervention group were lower than in the control group ($P < 0.05$). After 2, 4, and 6 wk of treatment, the number of false responses, number of persistent bugs, and total responses in the WCST were significantly lower in the intervention group than in the control group ($P < 0.05$), and the amount of completed classification was significantly higher than in the control group ($P < 0.05$). After 2, 4, and 6 wk of therapy, the SSPI scores were significantly greater than those of the controls ($P < 0.05$). After 6 wk of treatment, the efficacy rates of the control and intervention groups were 81.67% and 91.67%, respectively. The curative effect in the intervention group was significantly higher than that in the control group ($P < 0.05$).

CONCLUSION

CCRT can significantly improve cognitive function and social abilities in patients with chronic schizophrenia.

Key Words: Computerized cognitive correction therapy; Schizophrenia; Cognitive function; Social function; Psychopathological factors

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Core Tip: Chronic schizophrenia is generally an unconscious disorder with obvious intellectual disabilities. Insidious onset, prolonged course, repeated aggravation or deterioration, and negative symptoms of mental illness are common manifestations of the disease. Cognitive function and social life ability are severely impaired. In this study, we investigated the effect of Computerized Cognitive Remediation Therapy on cognitive impairment and society using the Patient and Negative Syndrome Scale, Wisconsin Card Sorting Test, and Scale of Social Function in Psychosis Inpatients scores in 120 patients with chronic schizophrenia.

Citation: Hu JJ, Sun XR, Ni SM, Kong Y. Computerized cognitive remediation therapy on cognitive impairment and social function in patients with chronic schizophrenia. *World J Psychiatry* 2024; 14(6): 884-893

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/884.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.884>

INTRODUCTION

Schizophrenia is a common major mental disorder, the cause of which remains unclear[1]. According to relevant epidemiological investigations, schizophrenia affects a broad spectrum of patients and can occur in individuals of various age groups. It is complicated by mental activity abnormalities in many aspects, such as perception, thinking, behavior, and emotional responses. The disease course is characterized by prolonged and repeated episodes that seriously affect social and cognitive function[2]. More severe patients may also have suicidal and violent tendencies, endangering the lives of patients and others[3].

Currently, in addition to the two core symptoms of schizophrenia-positive and negative-a third symptom group has gradually entered the field of vision and gained attention among scholars in the field of psychiatry: Cognitive dysfunction[4]. Patients with chronic schizophrenia usually experience cognitive dysfunction because they cannot achieve complete remission of their clinical symptoms. Compared with the general population, patients with schizophrenia require long-term hospitalization because of the disease, and their social function is significantly reduced[5].

Clinically, schizophrenia is mainly treated with antipsychotic drugs; however, a single drug treatment can only control the mental symptoms of patients and does not have a significant impact on their cognitive and social features; the treatment requires a long duration and is prone to adverse reactions, resulting in poor treatment compliance[6]. Computerized Cognitive Remediation Therapy (CCRT) is a training method based on behavioral training that improves thinking abilities[7]. Studies have confirmed[8] that applying CCRT for cognitive improvement in patients can effectively improve language, memory, executive power, and other functions. This is because computer cognitive correction therapy is a type of rehabilitation software that is highly targeted for patients with schizophrenia. In the software system, training and intervention are carried out on the patients' working memory, attention, reasoning and problem-solving, processing speed, social cognitive, and computing abilities. The ability of each part of the patient to interfere in a modular manner enhances cognitive performance and social function. In conclusion, as a new therapy, CCRT can effectively enhance the cognitive dysfunction of patients, and the effect is significant; however, few reports are available on CCRT treatment in patients with chronic schizophrenia. Therefore, this study aimed to examine how computerized therapy corrects cognitive deficits and affects the social functioning of patients with chronic schizophrenia.

MATERIALS AND METHODS

General information

One hundred and twenty patients with chronic deficit schizophrenia diagnosed at Shanghai Pudong New Area Mental Health Center between April 2021 and July 2022 were selected as study participants, including 69 males and 51 females, who were divided into an intervention (60 patients) and control groups (60 patients). Inclusion criteria: (1) All participants met the diagnostic criteria for schizophrenia[9]; (2) stable symptoms, current maintenance treatment with comparable antipsychotic medication, and Positive and Negative Symptom Scale (PANSS) scores of ≤ 70 ; (3) hospitalization > 2 times, with a total duration of illness of 2-10 years; age of 20-58 years old, and age of education > 8 years old; and (4) complete clinical data on patients. The exclusion criteria were as follows: (1) Comorbid chronic organic diseases; (2) mental and learning disabilities; (3) psychoactive substance use disorders or alcohol addiction; and (4) pregnant or lactating women.

Method

The control group was administered a small dose of the atypical antipsychotic drug lorazepam (Jiangsu Enhua Pharmaceutical Co., Ltd., State Pharmaceutical License H20223573, 10 mg) at a dosage of 10 mg/d once daily. Handicrafts, recreational activities, health exercises, playing poker, and watching television were also used for routine treatment. The intervention group used CCRT to provide therapeutic interventions to the patients based on the control group, which comprised four parts: Planning training, social cognition, working memory, and cognitive flexibility, each of which comprised 8-16 exercises, each of which had 8-16 cognitive correction tasks with different levels of difficulty. Patients were first trained by nurses on CCRT-related knowledge and computer operation. Under the therapist's guidance, the CCRT treatment underwent a structured sequence, starting with cognitive flexibility exercises designed to improve the ability to adapt to changing rules and situations. These tasks varied in difficulty and enhanced the patient's responsiveness to diverse cognitive demands. Next, the working memory was targeted with exercises like n-back tasks, where the complexity increased as patients demonstrated improved recall capabilities. This was followed by planning training, using strategic tasks such as the Tower of London, gradually intensifying the challenge to bolster problem-solving skills. The final component, social cognition, involved identifying emotions and interpreting social cues through progressively complex scenarios to enhance interpersonal understanding and interactions. Each session was tailored to the individual patient's level, ensuring consistent cognitive engagement. The intervention was administered over 12 wk, with sessions held five times per week, each lasting 45 min. This structured approach, detailed in Figure 1, evaluated the sustained impact of CCRT on improving cognitive and social outcomes, offering insights into its long-term efficacy and broader applicability in non-pharmacological interventions for chronic schizophrenia.

Index evaluation

Efficacy, PANSS, Scale of Social Function in Psychosis Inpatients (SSPI), and Wisconsin Card Sorting Test (WCST) scores.

Judging standard

Psychiatric symptom: Patients' mental symptoms were evaluated using the three-factor model of the PANSS[10], which has 30 items and a total score between 30 and 210 points. There were 7 positive signs, 7 negative signs, and 16 general psychopathology signs. The higher the number, the more severe the condition.

Cognitive function: All patients were assessed for function using the WCST[11]. The WCST is a neuropsychological test comprising 128 responses and four stimulus cards. This test measures error responses (RE), perseverative response errors (RPE), response answers (RA), and categories completed (CC). Among them, the scores of the three indexes (RE, RPE, and RA) were inversely proportional to the cognitive operation score, and the higher the score, the worse the cognitive function. The index of CC is proportional to cognitive function rating, and the greater the score, the better cognitive function.

Social function: SSPI[12] assesses the social functioning of the two groups of patients. This scale comprises three factors: Daily living ability, activity and communication status, and social activity skills. The higher the total score on the SSPI and each factor score, the lower the social functional deficits.

Statistical method

Data were analyzed using SPSS version 26.0 statistical software. For measurement data, mean \pm SD was used (\pm SD), and for inter-group comparisons, *t*-test was applied. Counting data are shown as percentages, and comparisons between groups were assessed using a chi-square test. Correlations were analyzed using Pearson's coefficients, and $P < 0.05$ displays a significant difference.

RESULTS

Comparison of clinical data gap in two groups

The general data of the two patient groups were compared, and the differences were not statistically significant ($P > 0.05$; Table 1).

Table 1 Comparison of general data between the two groups, *n* (%)

Item	Intervention group (<i>n</i> = 60)	Control group (<i>n</i> = 60)	<i>t</i>	<i>P</i> value
Sex ratio			1.67	1.96
Male	38 (63.3)	31 (51.67)		
Female	22 (36.7)	29 (48.33)		
Age (yr)	45.11 ± 10.37	46.14 ± 9.97	-0.58	0.57
Nation			0	1
Han nationality	55 (91.67)	55 (91.67)		
Other	5 (8.33)	5 (8.33)		
Duration of disease (yr)	9.26 ± 3.02	9.36 ± 3.74	-0.16	0.87
Number of hospitalizations (times)	3.97 ± 1.63	4.13 ± 1.42	-0.58	0.56
Years of schooling (yr)	9.97 ± 1.71	10.03 ± 1.36	-0.23	0.82
Smoking history			0.13	0.72
Exist	32 (53.33)	30 (50.00)		
None	28 (46.67)	30 (50.00)		
Drinking history			0.33	0.56
Exist	22 (36.67)	19 (31.67)		
None	38 (66.3)	41 (68.33)		0.56
Marital status			0.33	0.67
Married	41 (68.33)	38 (63.33)		
Unmarried	19 (31.67)	22 (36.67)		
Fertility			0.19	0.66
Infertile	13 (21.67)	16 (26.67)		
Rear	47 (78.33)	44 (73.33)		
SBP (mmHg)	128.06 ± 15.03	129.81 ± 18.28	-0.57	0.56
DBP (mmHg)	80.53 ± 12.41	83.15 ± 11.40	-1.2	0.23
HR	75.09 ± 15.98	77.51 ± 14.78	-0.87	0.39
Educational level			0.39	0.53
Less than high school	27 (45.00)	24 (40.00)		
High school and above	33 (55.00)	36 (60.00)		
BMI (kg/m ²)	21.16 ± 1.23	21.31 ± 1.41	-0.64	0.53
Family history of mental illness			0.87	0.35
Exist	26 (43.33)	21 (35.00)		
None	34 (56.67)	39 (65.00)		
Professional status			0.3	0.58
Incumbency	28 (46.67)	25 (41.67)		
Non-working	32 (53.33)	35 (58.33)		
Residence			0.03	0.85
Towns	33 (55.00)	34 (56.67)		
Countryside	27 (45.00)	26 (43.33)		
Forms of onset			0.55	0.46
Acute onset	23 (38.33)	27 (45.00)		
Chronic onset	37 (61.67)	33 (55.00)		

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; BMI: Body mass index.

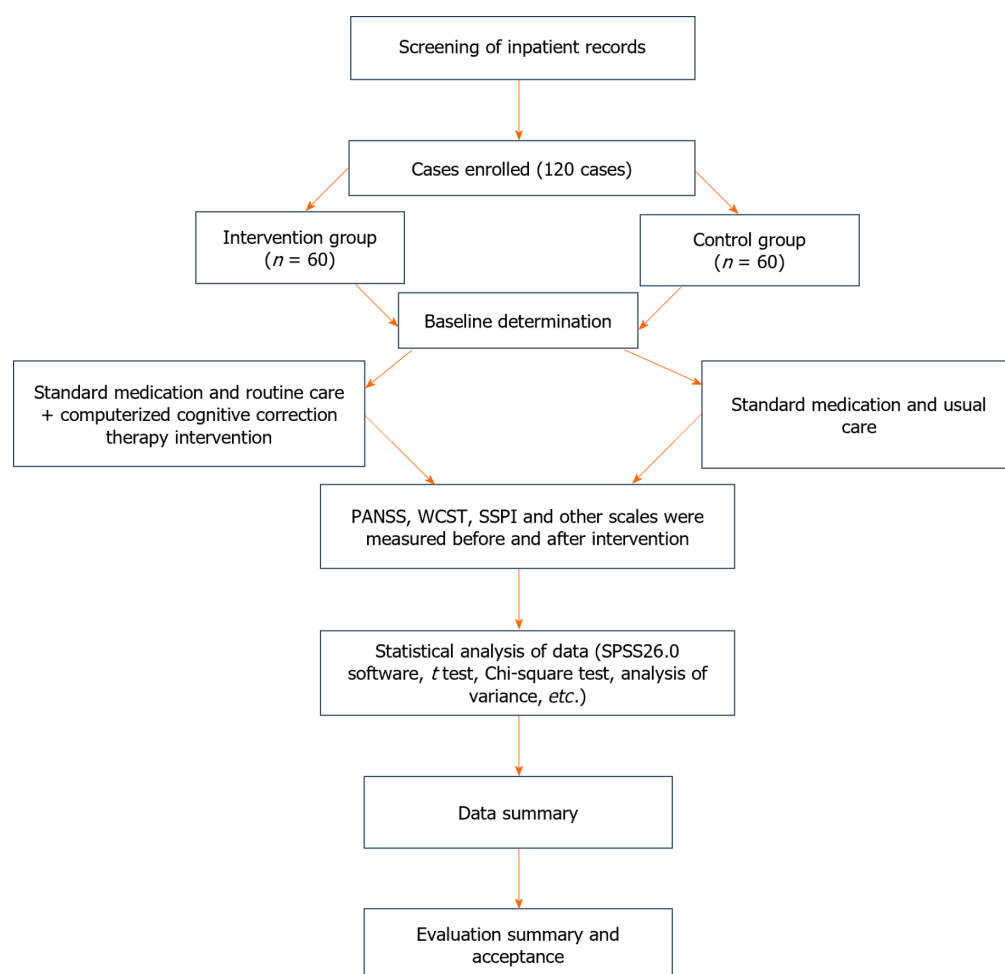


Figure 1 Technical route flow chart. PANSS: Positive and Negative Syndrome Scale; WCST: Wisconsin card sorting test; SSPI: Scale of social function in psychosis inpatients.

Comparison of PANSS scores before and after therapy gap in the two groups

The differences in PANSS scores between the control and intervention groups before treatment were not statistically significant ($P > 0.05$). After 2, 4, and 6 wk of treatment, significant decreases were observed in positive symptoms, negative symptoms, common psychopathological symptoms, and total PANSS scores in both groups compared to those before treatment ($P < 0.05$), and the decreases in the intervention group were greater than those in the control group. Differences were considered statistically significant (Table 2 and Figure 2).

Comparison of WCST pre- and post-therapy gap in the two groups

Before treatment, no significant difference was observed between the control and intervention groups in the RE, RPE, RA, and CC levels ($P > 0.05$); however, after 2-6 wk of continuous treatment, the amount of CC gradually increased. The RE, RPE, and RA scores of the intervention group gradually decreased, and the intervention group was significantly lower than the control group ($P < 0.05$), and the difference was statistically significant. Further details are provided in Table 3 and Figure 3.

Comparison of the curative effect gap in the two groups

In the control group, after 6 wk of treatment, 10 cases were cured, 22 cases were improved, 17 cases were better, and 11 cases were invalid, with an effective rate of 81.67%. In the intervention group, after 6 wk of treatment, 24 cases were cured, 18 were significantly improved, 13 were improved, and 5 were invalid, with an effective rate of 91.67%. The treatment efficiency in the intervention group was significantly better than that in the control group ($P < 0.05$), and the difference was statistically significant ($P < 0.05$; Table 4).

Comparison of SSPI scoring before and after treatment for the two groups

Before treatment, no statistically significant difference was observed between the SSPI scores of the two groups ($P > 0.05$);

Table 2 Comparison of positive and negative syndrome scale scores before and after treatment between the two groups of patients (mean \pm SD)

Times	Groups	General pathology	Positive symptom	Negative symptom	Totals
Pre-treatment	Intervention group (<i>n</i> = 60)	35.63 \pm 2.03	17.77 \pm 1.50	22.58 \pm 1.95	68.65 \pm 7.63
	Control groups (<i>n</i> = 60)	36.02 \pm 1.31	17.63 \pm 1.58	22.28 \pm 1.33	66.25 \pm 6.94
2 wk of treatment	Intervention group (<i>n</i> = 60)	26.22 \pm 2.49 ^a	11.85 \pm 2.29 ^a	15.63 \pm 1.59 ^a	53.70 \pm 3.46 ^a
	Control groups (<i>n</i> = 60)	33.42 \pm 3.34	15.12 \pm 1.84	18.18 \pm 3.65	64.72 \pm 5.53
4 wk of treatment	Intervention group (<i>n</i> = 60)	20.39 \pm 2.08 ^a	10.35 \pm 2.91 ^a	10.13 \pm 1.55 ^a	48.65 \pm 2.67 ^a
	Control groups (<i>n</i> = 60)	30.28 \pm 1.44	12.45 \pm 3.08	17.31 \pm 3.26	61.50 \pm 2.17
6 wk of treatment	Intervention group (<i>n</i> = 60)	12.21 \pm 5.72 ^a	7.18 \pm 6.48 ^a	9.12 \pm 1.79 ^a	43.02 \pm 7.62 ^a
	Control groups (<i>n</i> = 60)	23.85 \pm 5.67	10.90 \pm 2.36	11.91 \pm 2.09	56.95 \pm 6.94

^a*P* < 0.05, compared with pretreatment.

PANSS: Positive and negative syndrome scale.

Table 3 Comparison of Wisconsin Card Sorting Test scores before and after treatment between the two groups of patients (mean \pm SD, *n* = 60)

Times	Groups	RE	RPE	RA	CC
Pre-treatment	Intervention group	62.38 \pm 1.76	37.28 \pm 1.26	103.60 \pm 1.76	3.33 \pm 0.89
	Control groups	62.85 \pm 3.63	37.48 \pm 1.20	103.35 \pm 1.88	3.28 \pm 0.80
2 wk of treatment	Intervention group	53.23 \pm 2.06 ^a	25.07 \pm 2.39 ^a	90.20 \pm 4.28 ^a	4.03 \pm 0.84 ^a
	Control groups	56.73 \pm 3.68	32.62 \pm 4.39	97.65 \pm 5.43	3.97 \pm 0.89
4 wk of treatment	Intervention group	47.04 \pm 1.66 ^a	18.21 \pm 3.19 ^a	82.46 \pm 3.53 ^a	5.86 \pm 2.07 ^a
	Control groups	54.35 \pm 1.20	29.47 \pm 2.82	95.88 \pm 2.34	4.78 \pm 2.76
6 wk of treatment	Intervention group	39.92 \pm 2.29 ^a	10.50 \pm 3.68 ^a	75.89 \pm 1.58 ^a	7.42 \pm 2.24 ^a
	Control groups	52.24 \pm 3.71	25.41 \pm 1.36	91.92 \pm 4.39	6.23 \pm 1.72

^a*P* < 0.05, compared with pretreatment.

RE: Errors responses; RPE: Perseverative responses errors; RA: Responses answer; CC: Categories completed; WCST: Wisconsin card sorting test.

Table 4 Comparison of therapeutic efficacy between the two groups of patients, *n* (%)

Groups	Precedent	Heal	Significant progress	Progress	Null
Intervention group	60	24 (40.00)	18 (30.00)	13 (21.67)	5 (8.33)
Control groups	60	10 (16.67)	22 (36.67)	17 (28.33)	11 (18.33)
<i>t</i>					8.95
<i>P</i> value					0.03

after treatment, the daily living skills, motivation and socialization, social mobility skills, and SSPI total scores of the two groups were higher than those before treatment, and the intervention group had significantly higher scores than the control group (*P* < 0.05). After treatment, the daily living skills, motivation and socialization, social mobility skills, and SSPI total scores of both groups were higher than before treatment, and the intervention group had higher scores than the control group (Table 5 and Figure 4).

DISCUSSION

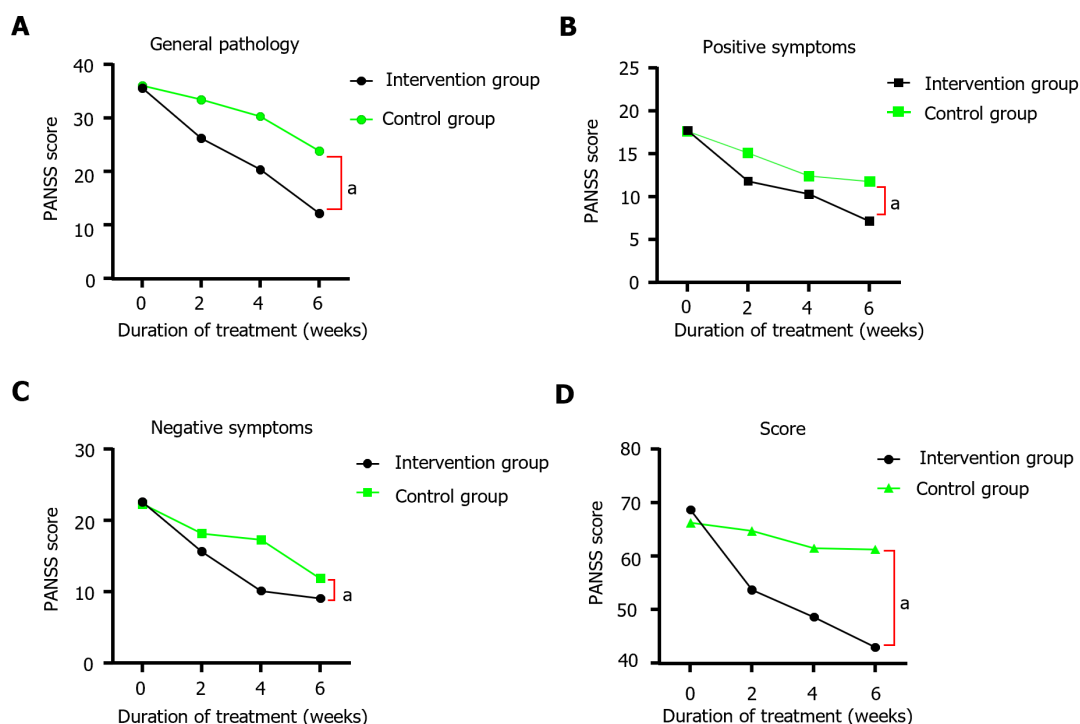
Deficit schizophrenia is a distinct subtype of schizophrenia that is characterized by primary and persistent negative

Table 5 Comparison of Social Functioning Scale for Psychiatric Inpatients scores before and after treatment between the two groups of patients

Times	Groups	Daily living skills	Motivation and socialization	Social mobility skills	SSPI total score
Pre-treatment	Intervention group (<i>n</i> = 60)	6.15 ± 2.22	9.15 ± 2.31	7.04 ± 1.14	9.15 ± 2.31
	Control groups (<i>n</i> = 60)	6.52 ± 1.99	8.81 ± 2.44	6.62 ± 3.59	8.81 ± 2.44
2 wk of treatment	Intervention group (<i>n</i> = 60)	11.06 ± 4.56 ^a	15.96 ± 3.80 ^a	11.99 ± 4.47 ^a	15.96 ± 3.80 ^a
	Control groups (<i>n</i> = 60)	8.00 ± 3.29	12.19 ± 3.78	8.03 ± 2.21	12.19 ± 3.78
4 wk of treatment	Intervention group (<i>n</i> = 60)	14.97 ± 3.29 ^a	18.85 ± 2.68 ^a	13.01 ± 2.95 ^a	18.85 ± 2.68 ^a
	Control groups (<i>n</i> = 60)	11.32 ± 2.79	15.72 ± 2.63	10.79 ± 2.78	15.72 ± 2.63
6 wk of treatment	Intervention group (<i>n</i> = 60)	21.32 ± 1.29 ^a	27.92 ± 5.80 ^a	19.13 ± 4.68 ^a	25.66 ± 5.45 ^a
	Control groups (<i>n</i> = 60)	14.78 ± 3.77	17.69 ± 3.51	14.13 ± 4.29	18.84 ± 3.98

^a*P* < 0.05, compared with pretreatment.

SSPI: Scale of Social Function in Psychotic Inpatients.

**Figure 2 Comparison of positive and negative syndrome scale scores before and after treatment between the two groups of patients.** A: Changes in general psychopathological symptom scores before and after treatment in both groups; B: Changes in scores of positive symptoms before and after treatment; C: Changes in scores of negative symptoms before and after treatment; D: Changes in total positive and negative syndrome scale scores before and after treatment in both groups. ^a*P* < 0.05. PANSS: Positive and Negative Syndrome Scale.

symptoms[13]. Currently, cognitive dysfunction in patients with schizophrenia and impairment mainly includes four types: Attention, abstract thinking, memory, and information integration disorders[14]. Cognitive impairment not only affects the rehabilitation of patients but also causes various aggressive behaviors in severe cases, which has important implications for patients' social skills and future well-being[15].

The study found that following 6 wk of CCRT treatment, significant improvement was observed in the general psychopathological factors and positive symptoms. The surgery group had lower PANSS scores and fewer negative symptoms than the control group, and the negative symptom score of the intervention group was more significantly decreased than that in the control group (*P* < 0.05). Currently, the primary treatment methods are modified electroconvulsive therapy and antipsychotic medication; however, the clinical efficacy of these two methods is limited. Compared with conventional treatment, computer cognitive correction therapy combined with drug therapy can not only significantly improve the cognitive and social functions of patients with schizophrenia but also improve their negative symptoms of patients [16,17]. After 6 wk of treatment, the number of false responses, sustained mistakes, and the total number of responses

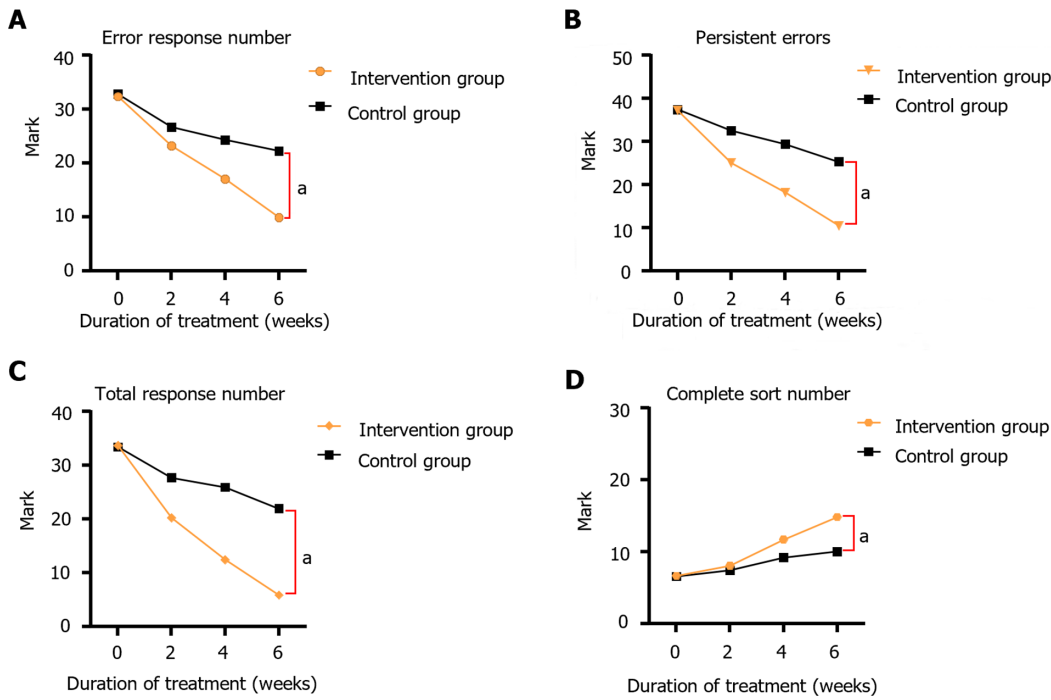


Figure 3 Comparison of Wisconsin Card Sorting Test scores before and after treatment between the two groups of patients. A: Change in the number of errors responses after treatment in both groups; B: Changes in the perseverative responses errors scores before and after treatment in both groups; C: Score changes in the number of patients with response answers before and after treatment in both groups; D: Changes in the number of categories completed before and after treatment in both groups. ^a $P < 0.05$. RE: Errors responses; RPE: Perseverative responses errors; RA: Response answers; CC: Categories completed.

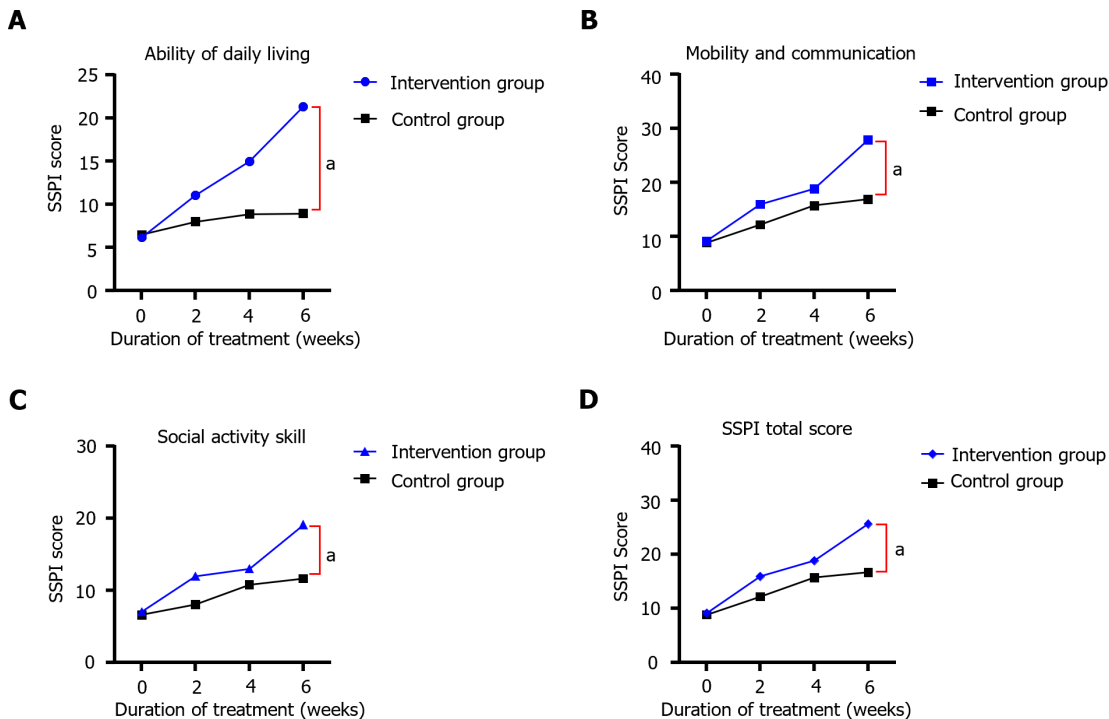


Figure 4 Comparison of Social Functioning Scale for Psychiatric Inpatients scores before and after treatment between the two groups of patients. A: Changes in daily living skills scores before and after treatment in both groups; B: Changes in the mobility and interaction scores before and after treatment in both groups; C: Changes in the social activity skill scores before and after treatment in both groups; D: Changes in the total Social Functioning Scale for Psychiatric Inpatients scores before and after treatment in both groups. ^a $P < 0.05$; SSPI: Scale of Social Function in Psychosis Inpatients.

were substantially reduced in the treated group compared to the uncontrolled group ($P < 0.01$). Computer cognitive correction therapy has been suggested to effectively improve the cognitive function of patients with chronic schizophrenia and is superior to conventional treatment. This indicates that patients with schizophrenia have greatly improved in many aspects of sensory perception after CCRT, which can significantly improve their working memory, task execution ability, and episodic memory ability and positively impact their attention and information processing efficiency [18]. After 6 wk of CCRT, the intervention group's SSPI score was significantly higher than that before treatment ($P < 0.05$); however, no significant change was observed in the control group ($P > 0.05$), and the curative effect in the intervention group was significantly higher than that in the control group ($P < 0.05$). Studies have shown that this treatment can improve brain activation and gray matter density, fundamentally altering neurobiological abnormalities that may be the root cause of cognitive dysfunction, suggesting that after significant improvement in cognitive correction therapy, patients significantly improve their social and cognitive abilities. It can also alleviate clinical symptoms, improve daily living abilities, and improve social activities [19,20]. After 6 wk of treatment, the actual rate of the control group was 81.67%. The effective rate of the intervention group was 91.67%. The curative effect of the intervention group was significantly higher than that of the control group ($P < 0.05$). These results indicate that CCRT can significantly improve clinical efficacy in patients with schizophrenia.

Summarily, CCRT treatment for patients with chronic deficit schizophrenia can not only improve their mental symptoms and cognitive function but also help improve their social function, which is worthy of clinical promotion and application. However, additional research is needed to understand its long-term effectiveness and applicability across different settings fully. Future studies should investigate the use of CCRT in varied demographic and geographic populations to determine its generalizability and effectiveness in diverse clinical environments. Moreover, the durability of the cognitive improvements post-treatment needs to be assessed. Long-term follow-up studies can help in determining whether the cognitive and social gains are sustained over extended periods, providing additional insights into the potential of CCRT as a routine intervention in the management of schizophrenia. This study had some limitations. First, because of the limitations of manpower, material resources, and other factors, this study only selected patients with schizophrenia from one hospital for research investigation; therefore, the sampling was not comprehensive enough. Second, the duration of computer cognitive correction therapy for patients was limited, with a maximum of six weeks. In subsequent studies, the duration of treatment should be extended, and patients should be followed up continuously after treatment to clarify the impact of long-term computer-assisted cognitive correction therapy on cognitive improvement in patients.

Additionally, in a follow-up study, the number of enrolled patients should continue to increase, and the sample size should be expanded to further increase the certainty of the treatment effect.

CONCLUSION

CCRT can effectively improve cognitive and social functions in patients with chronic schizophrenia and has a significant therapeutic effect.

FOOTNOTES

Author contributions: Hu JJ and Sun XR designed this study and analyzed the data; Kong Y conducted guiding work and critical review; Ni SM collected data and participated in the analysis; All authors approved the manuscript.

Supported by Shanghai Pudong New Area Science and Technology Development and Livelihood Research Special Fund Support Project, No. PKJ2023-Y80; and Integrated Traditional Chinese and Western Medicine Specialized Disease Diagnosis and Treatment Center Project, No. PDZY-2022-05-01.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of the Shanghai Pudong New Area Mental Health Center, No. PDJWLL2023023.

Informed consent statement: The Institutional Review Board approved the exemption from informed consent.

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

Data sharing statement: The data used in this study were obtained from the corresponding author upon request at ky_720@126.com.

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S-Editor: Li L

L-Editor: A

P-Editor: Chen YX

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Retrospective Study

Impact of thoracic paravertebral block and sufentanil on outcomes and postoperative cognitive dysfunction in thoracoscopic lung cancer surgery

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Yildirim OA, Türkiye

Received: March 12, 2024

Revised: May 13, 2024

Accepted: May 24, 2024

Published online: June 19, 2024

Processing time: 99 Days and 4.4 Hours



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Abstract

BACKGROUND

Postoperative pain management and cognitive function preservation are crucial for patients undergoing thoracoscopic surgery for lung cancer (LC). This is achieved using either a thoracic paravertebral block (TPVB) or sufentanil (SUF)-based multimodal analgesia. However, the efficacy and impact of their combined use on postoperative pain and postoperative cognitive dysfunction (POCD) remain unclear.

AIM

To explore the analgesic effect and the influence on POCD of TPVB combined with SUF-based multimodal analgesia in patients undergoing thoracoscopic radical resection for LC to help optimize postoperative pain management and improve patient outcomes.

METHODS

This retrospective analysis included 107 patients undergoing thoracoscopic radical resection for LC at The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital between May 2021 and January 2023. Patients receiving SUF-based multimodal analgesia ($n = 50$) and patients receiving TPVB + SUF-based multimodal analgesia ($n = 57$) were assigned to the control group and TPVB group, respectively. We compared the Ramsay Sedation Scale and visual analog scale (VAS) scores at rest and with cough between the two groups at 2, 12, and 24 h after surgery. Serum levels of epinephrine (E), angiotensin II (Ang II), norepinephrine (NE), superoxide dismutase (SOD), vascular endothelial growth factor (VEGF), transforming growth factor- β 1 (TGF- β 1), tumor necrosis factor- α (TNF- α), and S-100 calcium-binding protein β (S-100 β) were measured before and

24 h after surgery. The Mini-Mental State Examination (MMSE) was administered 1 day before surgery and at 3 and 5 days after surgery, and the occurrence of POCD was monitored for 5 days after surgery. Adverse reactions were also recorded.

RESULTS

There were no significant time point, between-group, and interaction effects in Ramsay sedation scores between the two groups ($P > 0.05$). Significantly, there were notable time point effects, between-group differences, and interaction effects observed in VAS scores both at rest and with cough ($P < 0.05$). The VAS scores at rest and with cough at 12 and 24 h after surgery were lower than those at 2 h after surgery and gradually decreased as postoperative time increased ($P < 0.05$). The TPVB group had lower VAS scores than the control group at 2, 12, and 24 h after surgery ($P < 0.05$). The MMSE scores at postoperative days 1 and 3 were markedly higher in the TPVB group than in the control group ($P < 0.05$). The incidence of POCD was significantly lower in the TPVB group than in the control group within 5 days after surgery ($P < 0.05$). Both groups had elevated serum E, Ang II, and NE and decreased serum SOD levels at 24 h after surgery compared with the preoperative levels, with better indices in the TPVB group ($P < 0.05$). Marked elevations in serum levels of VEGF, TGF- β 1, TNF- α , and S-100 β were observed in both groups at 24 h after surgery, with lower levels in the TPVB group than in the control group ($P < 0.05$).

CONCLUSION

TPVB combined with SUF-based multimodal analgesia further relieves pain in patients undergoing thoroscopic radical surgery for LC, enhances analgesic effects, reduces postoperative stress response, and inhibits postoperative increases in serum VEGF, TGF- β 1, TNF- α , and S-100 β levels. This scheme also reduced POCD and had a high safety profile.

Key Words: Thoracic paravertebral block; Sufentanil; Thoracoscope; Radical resection of lung cancer; Postoperative cognitive dysfunction

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Core Tip: This study demonstrates that the combination of thoracic paravertebral block with sufentanil-based multimodal analgesia in patients undergoing thoroscopic surgery for lung cancer (LC) enhances analgesia and reduces the rate of postoperative cognitive dysfunction. Besides decreasing postsurgical stress responses and various serum biomarker levels, this combination scheme exhibits higher safety, potentially providing a more effective strategy for pain management and cognitive function preservation. Our findings pave the way for new standards in postoperative care for LC surgery.

Citation: Wang DD, Wang HY, Zhu Y, Lu XH. Impact of thoracic paravertebral block and sufentanil on outcomes and postoperative cognitive dysfunction in thoroscopic lung cancer surgery. *World J Psychiatry* 2024; 14(6): 894-903

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/894.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.894>

INTRODUCTION

The incidence of malignancies in China accounts for approximately 21.8% of cases worldwide[1]. Among all malignant tumor types, lung cancer (LC) ranks first in men and second in women, with a standardized mortality rate of 39.81 per 100000 population, which is the highest among all cancer types[2]. Although there are various treatment strategies for LC, surgery is considered the key approach and has been the preferred strategy in clinical practice in recent years. This is mainly due to rapid developments in minimally invasive thoroscopic technology and its widespread clinical use[3]. Compared with traditional thoracotomy, minimally invasive thoroscopic surgery involves smaller incisions and results in less trauma, milder pain, and faster postoperative recovery.

Patients undergoing thoroscopic radical resection for LC usually receive a single general anesthesia that requires large doses of analgesic and sedative drugs and may greatly impact the cardiovascular and immune systems as well as postoperative cognitive function in older adults[4]. However, single general anesthesia cannot completely block the pain stimulation from the surgical area, potentially leading to an excessive stress reaction and an increased risk of postoperative complications and tumor recurrence and metastasis. Furthermore, although thoroscopic surgery is minimally invasive, it still affects respiratory and circulatory function, thus affecting postoperative recovery[5]. Some patients are afraid to cough after surgery due to concerns about pain, resulting in delayed sputum discharge and reduced effective breathing times, leading to lung infection and atelectasis[6]. Therefore, the determination of an ideal analgesic method that relieves postoperative pain and reduces the rate of complications is crucial. Sufentanil (SUF)-based multimodal analgesia has a good analgesic effect, rapid onset, and little influence on cardiovascular function, making it a relatively ideal analgesic[7,8]. However, the analgesic effect may also be influenced by the number of drainage tubes,

incision length, and other factors, resulting in unstable pain relief[9]. The single administration of a thoracic paravertebral block (TPVB) has been reported to relieve pain in intercostal incisions by blocking multiple intercostal nerves[10].

The effect of TPVB combined with SUF analgesia on patients undergoing thoracoscopic radical surgery for LC and its influence on postoperative cognitive dysfunction (POCD) is rarely reported, and the effect of this scheme on postoperative pain and cognitive dysfunction requires clarification. Therefore, the purpose of this study was to analyze the effects of TPVB combined with SUF-based multimodal analgesia on the analgesic effect and postoperative cognitive function of patients undergoing thoracoscopic radical surgery for LC to provide potential solutions for clinical treatment.

MATERIALS AND METHODS

Data collection

We retrospectively analyzed data on 107 patients who underwent thoracoscopic radical surgery for LC in The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital from May 2021 to January 2023. Patients were grouped into a TPVB group ($n = 57$) and a control group ($n = 50$) according to the different anesthesia schemes.

Criteria for patient enrollment and exclusion

Patients aged ≥ 18 years diagnosed with LC who met the criteria for thoracoscopic radical resection and received surgical treatment, with normal preoperative coagulation function test results, American Society of Anesthesiologists physical status[11] grade I or II, clear consciousness, normal communication skills, and no distant metastasis were included in the study population.

Patients with the inability to communicate normally and cooperate with the research process due to language comprehension disorders and mental illness and those with severe cardiocerebrovascular diseases, history of preoperative radiotherapy and chemotherapy, history of other surgeries, deformity of the spine or thorax, and diseases of the immune system or central nervous system were excluded from the study population.

Surgical protocols

Patients in both groups underwent routine preoperative medical examinations, including routine blood, coagulation function, and urine tests, as well as an electrocardiogram. General anesthesia was administered prior to surgery using the following anesthetic drugs: midazolam (0.3 mg; Yichang Humanwell Pharmaceutical Co., Ltd.), SUF (0.3 $\mu\text{g}/\text{kg}$; Jiangsu Nhwa Pharmaceutical Co., Ltd.), etomidate (0.3 mg/kg; Jiangsu Enhua), and cisatracurium (0.25 mg/kg; Zhejiang Xianju Pharmaceutical Co., Ltd.). Routine endotracheal intubation and mechanical ventilation were performed, with sevoflurane (0.8–1.5 MAC; Fujian Highsea United Pharmaceutical Co., Ltd.), propofol (2.6–3.2 $\mu\text{g}/\text{kg}$; Beijing Scieure Pharmaceutical Co., Ltd.), and remifentanyl (0.3 $\mu\text{g}/\text{kg}/\text{min}$; Jiangsu Nhwa Pharmaceutical Co., Ltd.) used to maintain anesthesia. Cisatracurium (0.1 mg/kg) was administered intermittently, depending on the patient's condition. The patient's vital signs were closely monitored during the operation, and the drug dosage was adjusted accordingly. For the control group, SUF-based multimodal analgesia was administered after surgery, and patient-controlled intravenous analgesia was connected, where 100 μg SUF and 5 mg tropisetron (Shandong Luoxin Pharmaceutical Group Stock Co., Ltd.) were diluted with 100 mL normal saline for pumping. The TPVB group received a TPVB and SUF-based multimodal analgesia, with the latter being the same as that of the control group. For the TPVB, the patient was placed on their side before anesthesia, and a puncture point was selected in the T4–T7 paraspinal space on the operating side. The paravertebral nerve block was then performed with an atraumatic needle for peripheral nerve blocks under ultrasound guidance. When the needle reached below the transverse process, 0.5% ropivacaine (15 mL; Chengdu Baiyu Pharmaceutical Co., Ltd.) was injected, and the absence of cerebrospinal fluid, blood, and air was confirmed.

Clinical data collection

Clinical data and laboratory test results were collected from patients' electronic medical records and surgical records, respectively. The clinical data included age, sex, pathological stage, pathological type, operation time, intraoperative blood loss, and history of diabetes and hypertension. The laboratory indices included epinephrine (E), norepinephrine (NE), angiotensin II (Ang II), superoxide dismutase (SOD), vascular endothelial growth factor (VEGF), transforming growth factor- β 1 (TGF- β 1), tumor necrosis factor- α (TNF- α), and S-100 calcium-binding protein β (S-100 β). The functional scores used included the Mini-Mental State Examination (MMSE)[12], the Ramsay Sedation Scale[13], and the visual analog scale (VAS)[14].

Detection method and functional score

Before and 24 h after surgery, 5 mL of cubital venous blood was collected from all patients and centrifuged at 3000 rpm for 10 min. The resultant serum was stored at -70°C for later testing. E and NE were determined using radioimmunoassay (Shanghai Xinfan Biotechnology Co., Ltd.), Ang II using chemiluminescence assay (Shenzhen Snibe Biomedical Engineering Co., Ltd.), and SOD, VEGF, TGF- β 1, TNF- α , and S-100 β using enzyme-linked immunosorbent assay (Hangzhou Haoxin Biotechnology Co., Ltd.).

Cognitive function was assessed using the MMSE (scale: 0–30). A score of 2 points lower than that on the day before surgery was considered an indicator of POCD. The Ramsay sedation score was determined as follows: anxious and restless, 1 point; tranquil and cooperative, 2 points; somnolent with prompt response to instructions, 3 points; light sleep with quick response to arousal, 4 points; sleeping with slow response to arousal, 5 points; and deep sleep with no

response to arousal, 6 points. A score of 1, 2-4, and ≥ 5 indicated insufficient sedation, good sedation, and excessive sedation, respectively. Pain was assessed using the VAS. The score ranges from 0 to 10 and is directly proportional to the pain level.

Outcome measures

The primary outcome measures were differences in MMSE scores before surgery and 3 and 5 days after surgery, as well as differences in Ramsay Sedation Scale and VAS scores at 2, 12, and 24 h after surgery.

The secondary outcome measures included changes in VEGF, TGF- β 1, TNF- α , S-100 β , and stress function indices between the two groups before and after treatment. The number of adverse reactions was also reported.

Statistical analysis

All analyses were performed using SPSS v19 statistical software. *P* values < 0.05 were considered statistically significant. Quantitative data were expressed as mean \pm SD. Paired *t*-test and independent sample *t*-test were used for intragroup and intergroup comparisons, respectively. analysis using Bonferroni test. Continuous data were expressed as numbers and rates. Multiple time point comparisons were conducted using repeated measures ANOVA, and post hoc (%). χ^2 tests were performed for categorical data.

RESULTS

Comparison of baseline data

There were no statistically significant differences in age, sex, pathological stage, pathological type, operation time, intraoperative blood loss, diabetes history, and hypertension history between the control and TPVB groups ($P > 0.05$; Table 1).

Changes in MMSE scores

There was no statistically significant difference in the pretreatment MMSE scores between groups ($P > 0.05$). The MMSE scores of both groups were significantly lower on postoperative day 3 than on the day before surgery ($P < 0.05$), with significantly higher MMSE scores in the TPVB group compared with the control group ($P < 0.001$). The MMSE score was higher in the TPVB group than in the control group ($P < 0.05$) on postoperative day 5. MMSE scores in both groups were significantly higher on postoperative day 5 than on postoperative day 3 ($P < 0.05$). However, there was no difference in the MMSE scores on postoperative day 5 compared with the day before surgery in the TPVB group ($P > 0.05$), while MMSE scores on postoperative day 5 were significantly decreased compared with the day before surgery in the control group with ($P < 0.05$; Table 2). Seven patients in the TPVB group and 15 patients in the control group developed POCD within 5 days after surgery, suggesting a lower probability of POCD in the TPVB group compared with the control group ($P < 0.05$).

Changes in Ramsay sedation scores

A comparison of the Ramsay scores at each time point revealed no statistical difference between the two groups ($P > 0.05$; Table 3).

Changes in VAS scores

A comparison of pre- and posttreatment VAS scores did not reveal any statistically significant intergroup differences at 2 h after surgery ($P > 0.05$). In both groups, the VAS scores decreased significantly at 12 h after surgery compared with 2 h after surgery ($P < 0.05$), with higher VAS scores in the TPVB group *vs* the control group ($P < 0.05$). At 24 h after surgery, the VAS score in the TPVB group was significantly lower than in the control group ($P < 0.05$). In both groups, the VAS score at 24 h after surgery was significantly lower than that at 12 h ($P < 0.05$) and at 2 h ($P < 0.001$) after surgery (Table 4).

Changes in stress function indices before and after treatment

We compared stress function indices of the two groups before and after treatment. There was no significant difference in preoperative levels of E, Ang II, NE, and SOD between the two groups ($P > 0.05$). In both groups, the levels of E, Ang II, and NE were significantly elevated at 24 h after surgery compared with their preoperative levels ($P < 0.0001$), while that of SOD decreased significantly ($P < 0.0001$). Moreover, the TPVB group had lower E, Ang II, and NE levels and higher SOD levels than the control group at 24 h after surgery ($P < 0.0001$; Figure 1).

Changes of VEGF, TGF- β 1, TNF- α , and S-100 β before and after treatment

We compared the pre- and posttreatment levels of VEGF, TGF- β 1, TNF- α , and S-100 β . The preoperative levels were similar between groups ($P > 0.05$). The levels of VEGF, TGF- β 1, TNF- α , and S-100 β were significantly increased in both groups at 24 h after surgery compared with the levels before surgery ($P < 0.01$). Moreover, the levels of VEGF, TGF- β 1, TNF- α , and S-100 β were significantly lower in the TPVB group than in the control group at 24 h after surgery ($P < 0.0001$; Figure 2).

Statistical analysis of adverse reactions

Differences in the occurrence of adverse reactions between the two groups were not statistically significant ($P > 0.05$;

Table 1 Comparison of baseline data					
Factors		TPVB group (n = 57)	Control group (n = 50)	χ^2/t test	P value
Age	≥ 60 years	31	31	0.633	0.426
	< 60 years	26	19		
Sex	Male	31	30	0.342	0.558
	Female	26	20		
Pathological stage	I	17	20	1.219	0.543
	II	28	21		
	III	12	9		
Pathological type	Squamous cell carcinoma	27	20	0.587	0.443
	Adenocarcinoma	30	30		
Operation time		147.35 ± 15.70	148.44 ± 13.30	0.384	0.701
Intraoperative blood loss (mL)		141.05 ± 54.49	131.14 ± 53.54	0.946	0.346
History of diabetes	Yes	10	12	0.679	0.409
	No	47	38		
History of hypertension	Yes	14	17	1.153	0.282
	No	43	33		

TPVB: Thoracic paravertebral block.

Table 2 Changes in Mini-Mental State Examination scores			
Grouping	Before surgery	3 days after surgery	5 days after surgery
TPVB group (n = 57)	28.51 ± 0.95	25.05 ± 1.20 ^a	27.56 ± 0.95 ^b
Control group (n = 50)	28.06 ± 1.27	23.42 ± 1.31 ^a	27.38 ± 0.85 ^{a,b}
t value	2.140	7.909	3.402
P value	0.499	< 0.001	0.016

^aP < 0.05 compared with the preoperative level.
^bP < 0.05 compared with the value at 3 days after surgery.
TPVB: Thoracic paravertebral block.

Table 5).

DISCUSSION

The prevalence and mortality of LC have continued to rise in recent years, seriously impacting the health and quality of life of those affected[15]. The older adult population has a high risk of LC development. Because they often suffer from multiple chronic diseases and have a relatively low tolerance for surgery and pain, the choice of an appropriate surgical modality is critical[16]. Compared with traditional thoracotomy, thoracoscopic radical resection for LC is less traumatic and has a faster recovery rate and fewer complications, making it the first choice for older adult patients. Although this

Table 3 Changes in Ramsay sedation scores

Grouping	2 h after surgery	12 h after surgery	24 h after surgery
TPVB group (<i>n</i> = 57)	2.91 ± 0.93	2.91 ± 0.74	2.70 ± 0.50
Control group (<i>n</i> = 50)	2.62 ± 0.64	2.66 ± 0.69	2.62 ± 0.49
<i>t</i> value	2.241	1.946	0.686
<i>P</i> value	0.388	0.791	0.945

TPVB: Thoracic paravertebral block.

Table 4 Visual analog scale score changes

Grouping	2 h after surgery	12 h after surgery	24 h after surgery
TPVB group (<i>n</i> = 57)	3.53 ± 0.6	2.68 ± 0.47 ^a	2.18 ± 0.38 ^{a,b}
Control group (<i>n</i> = 50)	3.42 ± 0.54	2.98 ± 0.14 ^a	2.5 ± 0.54 ^{a,b}
<i>t</i> value	1.064	3.318	3.632
<i>P</i> value	0.934	0.015	0.005

^a*P* < 0.05 compared with the preoperative level.

^b*P* < 0.05 compared with the value at 12 h after surgery.

TPVB: Thoracic paravertebral block.

Table 5 Statistical analysis of adverse reactions

Grouping	Nausea and vomiting	Hypotension	Delayed recovery from anesthesia	Respiratory depression
TPVB group (<i>n</i> = 57)	2	3	1	0
Control group (<i>n</i> = 50)	1	2	1	2
χ^2	0.222	0.095	0.001	2.323
<i>P</i> value	0.637	0.757	0.925	0.127

TPVB: Thoracic paravertebral block.

procedure reduces the major trauma associated with thoracotomy and enables intercostal puncture, intrathoracic manipulation, and thoracic drainage and indwelling, narcotic drugs still trigger a substantial stress response[17]. Such intense stress reactions stimulate the production of a large number of inflammatory factors, which may lead to hemodynamic disturbance and increase the risk of postoperative complications and tumor recurrence and metastasis[18]. Therefore, when choosing perioperative anesthesia, it is necessary to both enhance the analgesic effect and reduce patient stress, inflammation, and postoperative adverse reactions to improve postoperative recovery.

Combination analgesic schemes[19] can achieve a good analgesic effect because a variety of analgesic drugs can be used in combination to complement each other's mechanism of action during the perioperative period, thereby enhancing the analgesic effect and relieving postoperative pain. The SUF-based multimodal analgesia scheme has been widely used in surgical procedures. Although this scheme allows patients to relieve postoperative pain without the need for supplementary analgesia, there are some drawbacks, such as drug dependence in some patients with limited efficacy[20]. TPVB involves the injection of local anesthetic drugs that act on sympathetic nerves to achieve a local block. There is no obvious effect on hemodynamics, and the occurrence of respiratory depression is reduced[21]. Clinically, TPVB combined with SUF-based multimodal analgesia can be considered to relieve postoperative pain in patients undergoing thoracoscopic surgery for LC, and this may be a new and effective intervention scheme. Our study revealed that the TPVB group had higher MMSE scores on postoperative day 1 and day 3, a lower incidence of POCD, and no significant differences in the incidence of postoperative adverse reactions compared with the control group. Thus, the combined use of TPVB and SUF enhanced the analgesic effect, effectively reduced postoperative cognitive impairment, and lowered the rate of adverse reactions in older adult patients undergoing thoracoscopic surgery for LC, thereby reducing the impact on cognitive function.

The injection of local anesthetic drugs into the thoracic paravertebral space for a TPVB ensures the blocking of multiple ipsilateral somatic segments and sympathetic nerves[22]. Notably, ultrasound-guided block enables direct observation of the block site, thereby improving the puncture success rate and ensuring sufficient block, which shortens the onset time.

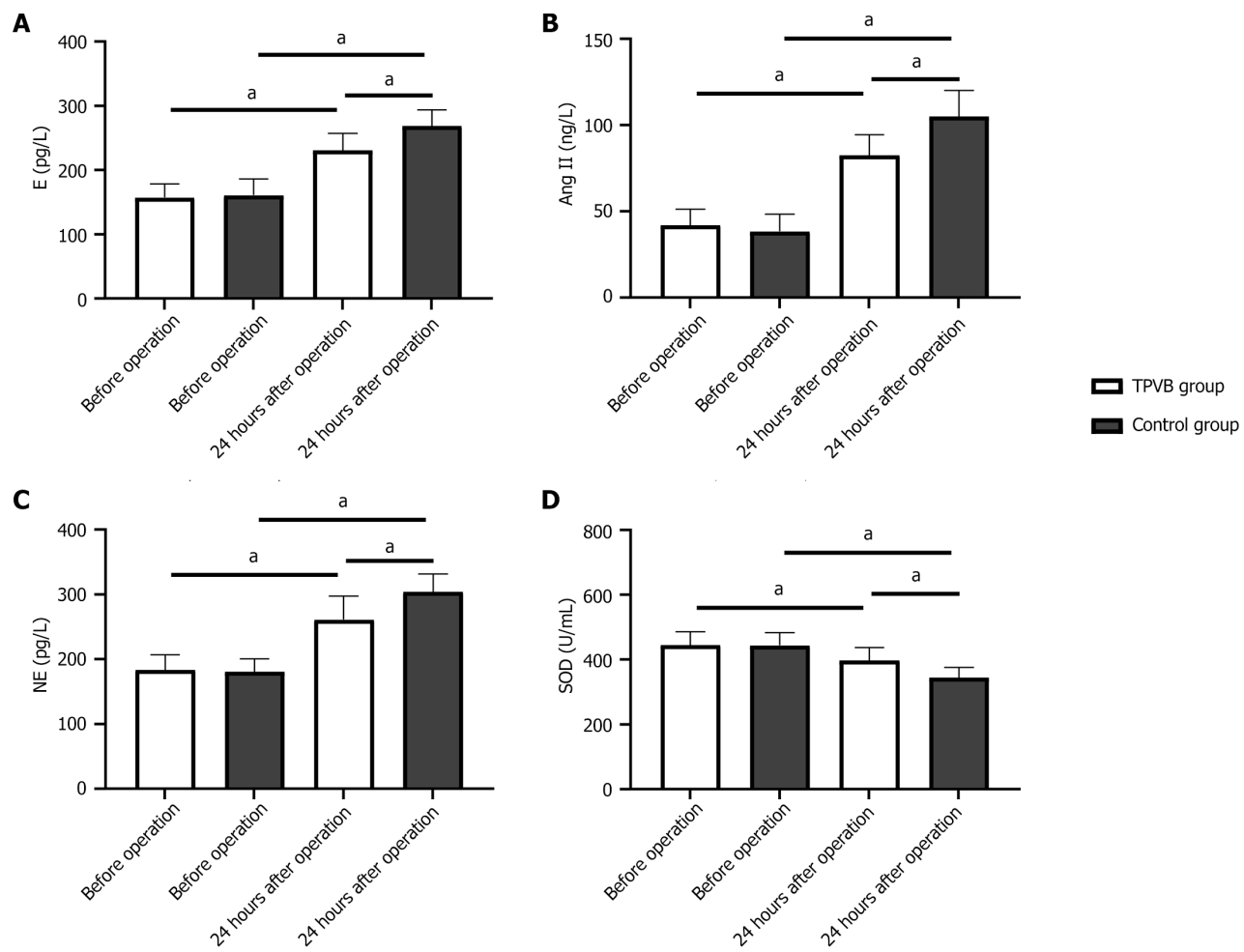


Figure 1 Changes in stress function indices of patients before and after surgery. A: Comparison of the changes in epinephrine levels before and after surgery; B: Comparison of the changes in angiotensin II levels before and after surgery; C: Comparison of the changes in norepinephrine levels before and after surgery; D: Comparison of the changes in superoxide dismutase levels before and after surgery. E: Epinephrine; Ang II: Angiotensin II; NE: Norepinephrine; SOD: Superoxide dismutase; * $P < 0.0001$.

We found that compared with the control group, the Ramsay sedation score in the TPVB group was almost the same at 2, 12, and 24 h after surgery, but the VAS score was significantly reduced. This suggests that TPVB combined with SUF-based multimodal analgesia not only achieves a good sedative effect but also enhances the analgesic effect. Additionally, ropivacaine, which has a prolonged action time, better local anesthetic effect than lidocaine, low fat solubility, and shorter recovery time of motor nerve block, is also used in TPVB, enabling patients to start bed activities as soon as possible[23]. The use of ropivacaine to perform TPVB combined with general anesthesia has also been shown to cover the sensory nerves at the surgical site more comprehensively to block the pain conduction pathway, thereby alleviating pain[24]. Therefore, in cases where SUF-based multimodal analgesia is ineffective, TPVB can be supplemented to reduce pain more effectively and enhance the analgesic effect[25].

It is well known that surgical injury and anesthesia may cause a stress response that triggers changes in endocrine hormones. Increases in the levels of stress hormones, such as NE and E, indicate increased sympathetic nerve activity, and their entry into the bloodstream may cause vasoconstriction and trigger hemodynamic instability[26]. Ang II activates the renin-angiotensin system and induces oxidative stress[27]. SOD exerts antioxidant effects by scavenging oxygen free radicals to reduce oxidative stress[28]. We found that the serum levels of E, Ang II, and NE in the two groups increased within 24 h after surgery, and the SOD level decreased, which was mainly due to the stress reaction caused by surgical injury. However, compared with the control group, serum levels of E, Ang II, and NE were lower and SOD was higher in the TPVB group, indicating that the treatment scheme used in the TPVB group alleviates the stress reaction. The main reason for this may be that TPVB combined with SUF-based multimodal analgesia further inhibits sympathetic nerve activity, thereby alleviating postoperative pain, promoting wound healing, and relieving postoperative stress.

VEGF and TGF- β 1 are key regulators of vascular proliferation that stimulate vascular division and proliferation and promote neovascularization, promoting the widespread distribution and metastasis of cancer cells[29]. The higher the levels of VEGF and TGF- β 1, the greater the risk of metastasis in cancer patients. When the body is under stress or in pain, TNF- α stimulates the release of neuroactive substances, which may exacerbate the inflammatory response, further damaging nerve function[30]. S-100 β participates in the degradation of the extracellular matrix, and the more serious the inflammatory reaction, the higher its level[31]. Our findings showed that the serum levels of VEGF, TGF- β 1, TNF- α , and

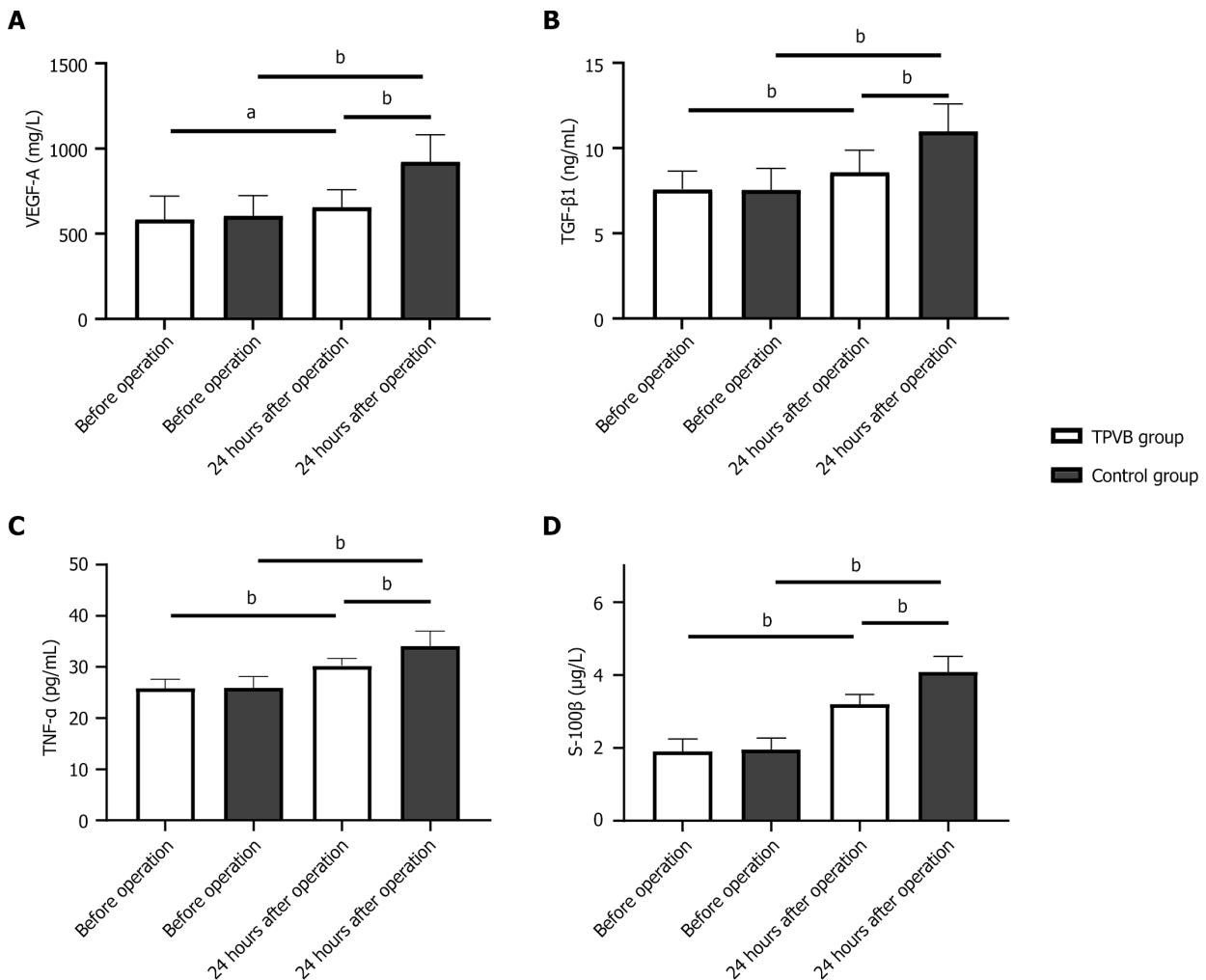


Figure 2 Changes of vascular endothelial growth factor, transforming growth factor-β1, tumor necrosis factor-α, and S-100 calcium-binding protein β before and after surgery. A: Comparison of the changes of vascular endothelial growth factor levels before and 24 h after surgery; B: Comparison of the changes of transforming growth factor-β1 levels before and 24 h after surgery; C: Comparison of the changes of tumor necrosis factor-α levels before and 24 h after surgery; D: Comparison of the changes of S-100 calcium-binding protein β levels before and 24 h after surgery. VEGF: Vascular endothelial growth factor; TGF-β1: Transforming growth factor-β1; TNF-α: Tumor necrosis factor-α; S-100β: S-100 calcium-binding protein β. ^a*P* < 0.01; ^b*P* < 0.0001.

S-100β were increased in both groups within 24 h after surgery. However, the levels were lower in the TPVB group, suggesting that TPVB combined with SUF-based multimodal analgesia inhibits the formation of new tumor blood vessels after surgery and alleviates inflammation. The rise in VEGF and TGF-β1 Levels may be caused by factors such as surgical procedures and local tissue pressure, which promote cancer cell spread, while the increased levels of TNF-α and S-100β are attributed to surgical injury-induced inflammatory reactions.

Our study confirmed the role of TPVB combined with SUF in preserving cognitive function and relieving pain in patients undergoing thoracoscopic radical resection for LC. However, there are some limitations that require further consideration. First, the sample size was limited due to the retrospective nature of the study. Second, because there was no follow-up, the influence of the two anesthesia schemes on patient prognosis requires further investigation. Therefore, prospective studies with adequate follow-up are necessary to validate our conclusions.

CONCLUSION

Our findings reveal the promising application of TPVB combined with SUF in thoracoscopic radical resection for LC. The combined scheme has an obvious analgesic effect and effectively reduces POCD risk, stress, and inflammation in older adults. This is highly beneficial for controlling pain, improving postoperative recovery, and reducing postoperative pain-induced stress responses.

FOOTNOTES

Author contributions: Wang DD designed the research and wrote the first manuscript; Wang DD, Wang HY, Zhu Y and Lu XH contributed to conceiving the research and analyzing data; Wang DD conducted the analysis and provided guidance for the research; all authors reviewed and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethic Committee of The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital.

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

Conflict-of-interest statement: Dr. Lu has nothing to disclose.

Data sharing statement: All data and materials are available from the corresponding author.

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Country of origin: China

ORCID number: Xi-Hua Lu 0009-0008-6215-2161.

S-Editor: Lin C

L-Editor: A

P-Editor: Chen YX

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Retrospective Study

Effect of a systemic intervention combined with a psychological intervention in stroke patients with oropharyngeal dysfunction

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade A

Scientific Significance: Grade B

P-Reviewer: De Man J, Belgium

Received: March 21, 2024

Revised: May 8, 2024

Accepted: May 15, 2024

Published online: June 19, 2024

Processing time: 89 Days and 22 Hours



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Abstract

BACKGROUND

Stroke frequently results in oropharyngeal dysfunction (OD), leading to difficulties in swallowing and eating, as well as triggering negative emotions, malnutrition, and aspiration pneumonia, which can be detrimental to patients. However, routine nursing interventions often fail to address these issues adequately. Systemic and psychological interventions can improve dysphagia symptoms, relieve negative emotions, and improve quality of life. However, there are few clinical reports of systemic interventions combined with psychological interventions for stroke patients with OD.

AIM

To explore the effects of combining systemic and psychological interventions in stroke patients with OD.

METHODS

This retrospective study included 90 stroke patients with OD, admitted to the Second Affiliated Hospital of Qiqihar Medical College (January 2022–December 2023), who were divided into two groups: regular and coalition. Swallowing function grading (using a water swallow test), swallowing function [using the standardized swallowing assessment (SSA)], negative emotions [using the self-rating anxiety scale (SAS) and self-rating depression scale (SDS)], and quality of life (SWAL-QOL) were compared between groups before and after the intervention; aspiration pneumonia incidence was recorded.

RESULTS

Post-intervention, the coalition group had a greater number of patients with grade 1 swallowing function compared to the regular group, while the number of patients with grade 5 swallowing function was lower than that in the regular group ($P < 0.05$). Post-intervention, the SSA, SAS, and SDS scores of both groups decreased, with a more significant decrease observed in the coalition group ($P < 0.05$). Additionally, the total SWAL-QOL score in both groups increased, with a more significant increase observed in the coalition group ($P < 0.05$). During the intervention period, the total incidence of aspiration and aspiration pneumonia in the coalition group was lower than that in the control group (4.44% *vs* 20.00%; $P < 0.05$).

CONCLUSION

Systemic intervention combined with psychological intervention can improve dysphagia symptoms, alleviate negative emotions, enhance quality of life, and reduce the incidence of aspiration pneumonia in patients with OD.

Key Words: Stroke; Oropharyngeal dysfunction; Systemic interventions; Psychological intervention; Curative effect; Negative emotion

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Core Tip: Patients with stroke combined with oropharyngeal dysfunction are prone to malnutrition, aspiration pneumonia, and psychological problems for an extended period, which are factors that indirectly contribute to disability and death. Through this investigation, we found that compared with conventional nursing, systemic intervention combined with a psychological intervention can effectively improve patients' swallowing function, relieve patients' anxiety and depression, and improve their quality of life.

Citation: Song J, Wang JD, Chen D, Chen J, Huang JF, Fang M. Effect of a systemic intervention combined with a psychological intervention in stroke patients with oropharyngeal dysfunction. *World J Psychiatry* 2024; 14(6): 904-912

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/904.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.904>

INTRODUCTION

Stroke is associated with a high rate of disability, and various dysfunctions often remain after onset. Oropharyngeal dysfunction (OD) is the most common complication of stroke[1]. It has been reported that the incidence of OD after stroke is 30%–65%[2]. Although some stroke patients can recover within a few weeks after stroke onset, between 11% and 50% of patients still experience OD after 6 months[3].

From the perspective of modern medicine, OD is believed to be caused by cerebral ischemia and hypoxia, leading to damage to the cortex, cortical bulbar tract, intracranial nerve, and glossopharyngeal nerve, and resulting in the loss of normal innervation of muscle groups and effectors by upper motor neurons[2,4]. The main clinical manifestations include obstruction during swallowing, inability to chew, difficulty in swallowing, coughing, aspiration, and food reflux. If timely intervention is not implemented, patients may develop water and electrolyte disorders, malnutrition, aspiration pneumonia, and severe suffocation directly[5,6]. At the same time, patients often experience psychological disorders such as panic, anxiety, and depression with respect to eating. These psychological issues are not only detrimental to the rehabilitation prognosis of stroke patients, but also increase the case fatality rate[7].

Studies have indicated that early identification of high-risk groups for swallowing disorders and active and effective preventive interventions can improve the clinical symptoms of patients and reduce long-term mortality[8].

Conventional nursing practices often lack individuality, resulting in suboptimal intervention effects in some patients. Systemic intervention is a relatively comprehensive nursing method involving systemic drug treatment and oral training to achieve an effective assessment of disease changes and improve diagnosis and treatment cooperation[9].

Clematis chinensis has the traditional use of dispelling wind dampness and promoting the circulation of channels and collaterals[10]. The "Compendium of Materia Medica" includes the use of *Clematis chinensis* in the treatment of "bone choking." Stroke patients with dysphagia experience excessive production of phlegm and saliva, discomfort in the pharynx, and obstruction of meridians and collaterals. The symptoms are similar to those of bone lumps. The effects of *Clematis chinensis* on gastrointestinal qi movement have been extended to the treatment of dysphagia[11].

Oral function training is based on the plasticity and repair ability of the central nervous system. Stimulating the oral intima to input sensory signals to the brainstem and cerebral cortex promotes the formation of new conduction pathways for related sensory-motor neurons and diseased nerve endings and reestablishes a motor reflex arc to promote the closure of the patient's lips and enhance the driving force of the tongue muscle[12]. Researchers have applied this rehabilitation method to older patients with dysphagia and stroke combined with OD, and the approach has been shown to promote their swallowing function and improve their quality of life[13]. Psychological interventions can provide psychological counseling for patients' psychological problems, effectively reduce psychological pressure, improve negative mood,

enhance patient compliance and confidence, and improve the effect of clinical interventions. However, there are few clinical reports on the application value of systemic intervention measures such as nebulizing inhalation of *Clematis chinensis* decoction combined with oral function training and psychological intervention in patients with swallowing disorders after stroke. In this study, we aimed to explore the effect of combining systemic and psychological interventions on the efficacy, negative emotions, and quality of life of stroke patients with OD.

MATERIALS AND METHODS

Participants

The retrospectively included 90 stroke patients with OD who were admitted from January 2022 and December 2023. The inclusion criteria were as follows: (1) Patients who met the diagnostic criteria for stroke[14] and dysphagia[15] who were diagnosed with stroke with OD by head computed tomography (CT) or magnetic resonance imaging (MRI); and (2) conscious, with normal communication skills. The exclusion criteria comprised the following comorbidities: (1) Immune system disease; (2) malignant tumor; (3) swallowing dysfunction caused by factors other than stroke; (4) serious diseases affecting important organs; (5) mental illness; and (6) critical conditions that precluded evaluation.

Based on differences in the intervention methods, the patients were divided into regular and coalition groups. The coalition group received a combination of systemic and psychological interventions. Each group consisted of 45 patients. There was no significant difference in the general data between the two groups ($P > 0.05$; Table 1).

Methods

The regular intervention group received routine nursing interventions, which included the following: (1) On the second day after admission, nurses performed a water-swallowing test to evaluate swallowing function; patients with dysphagia were fed a paste diet, and those with grade III dysphagia were fed *via* a nasogastric tube; (2) diet guidance was provided, including recommendations regarding eating position, paste food deployment, feeding methods, nasal feeding, and other matters; and (3) swallowing training was conducted, involving guiding family members to place their index and middle fingers on the patient's cricoid cartilage and instructing the patient to swallow. The pharynx was stimulated using a cold spoon.

Based on the regular group, the coalition group received systemic intervention measures combined with psychological interventions. The systemic intervention measures were as follows: (1) A traditional Chinese medicine intervention, which consisted of dried slices of *Clematis chinensis* Osbeck (Beijing Sanhe Pharmaceutical Co., Ltd.) decocted with 250 mL water for 5 min and then decocted for an additional 20 min. The decoction was prepared into 200 mL samples of Chinese medicine juice (containing 25 g raw *Clematis chinensis* Osbeck per 100 mL) and stored at 5 °C in the refrigerator. Ten milliliters of *Clematis chinensis* Osbeck liquid was administered twice daily *via* atomization until the liquid was depleted; (2) Oral swallowing function training was conducted by swallowing rehabilitation specialist nurses after atomization. These nurses evaluated the swallowing function of patients every day and provided one-to-one swallowing rehabilitation exercise training. The training included the following: lip movement, including lip-smashing, lip-spreading, lip-rounding, and lip muscle strength exercises (instructions consisted of asking the patient to close their lips and relax; instructing the patient to close their lips to forcefully close and pull out a tongue plate, which was alternately performed on the left and right sides, whilst concurrently engaging in confrontation training with the lips); tongue movement, tongue extension, tongue contraction, tongue rolling, tongue tip licking of the upper and lower lips, left and right mouth angle training, and tongue muscle resistance training; mandibular joint training, consisting of opening the mouth to the maximum, then relaxing, and moving the jaw to the left and right sides; tactile stimulation, with fingers, cotton swabs, tongue plate, toothbrush, and other items to stimulate the cheek inside and outside, lips, and the whole tongue to increase the sensitivity of these parts; taste stimulation, with different flavors of fruit juice or vegetable soup (*i.e.*, sour, sweet, bitter, spicy) to improve sensitivity and thereby promote appetite; and pharyngeal cold stimulation, consisting of gently touching the patient's soft palate and tongue root with an ice-cold cotton rod, and then performing empty swallowing training. Once a day, after completing a full training session, patients were encouraged to fully engage in their training; (3) Eating care, during which a swallowing rehabilitation specialist nurse assessed the nutritional status of the patient and calculated the total calories required. The daily intake target was set at a minimum of 80% of this amount, and meals were appropriately allocated. Patients took food into their mouth and adjusted it to a suitable viscosity. Infant rice flour was used to as a thickening paste, as needed[5]. There were three types of food: pudding, egg soup, and syrup. Pudding included thick and mashed meat porridge, vegetable puree, and fruit puree. Egg custard included steamed egg custard, bean flower, and bean curd brain, whereas the syrups included rice soup, juice drinks, and soy milk. For the pudding-like foods, 5 mL samples were tested with the patient, feeding at a slow rate, without speaking to the patient during the feeding process. The amount that constituted a comfortable mouthful was noted, with careful observation to address any choking or coughing by pausing feeding. Patients with nasal feeding were given mixed nutritional support: nutrient solution pumping and a self-made homogenized diet, with strict implementation of nasal feeding nursing points; and (4) Psychological intervention involved establishing a good trusting relationship with patients based on respect, sincerity, and empathy. Family members were asked to cooperate in this process. Through discussions about eating habits, patients' personalities and psychological characteristics were analyzed, and targeted intervention measures were formulated: patients were guided to engage in positive thinking and positive emotions through explanations and case guidance; patients were inspired to recall happy memories and share moments of happiness, such as their happiest past events and preferred hobbies; and patients were asked to remember three positive things every day and encouraged to include these memories in their rehabilitation exercises. Both groups received continuous intervention for 4 wk.

Table 1 Comparison of baseline data between the normal and coalition groups, *n* (%)

Group	Gender		Age (yr)	Course of disease (d)	Stroke type	
	Male	Female			Ischemic	Hemorrhagic
Coalition group (<i>n</i> = 45)	26 (57.78)	19 (42.22)	61.24 ± 8.97	13.11 ± 1.34	30 (66.67)	15 (33.33)
Regular group (<i>n</i> = 45)	24 (53.33)	21 (46.67)	62.33 ± 8.97	12.96 ± 1.40	27 (60.00)	18 (40.00)
χ^2/t	0.180		-0.576	0.540	0.431	
<i>P</i> value	0.671		0.566	0.591	0.512	

Survey tools

The following tools were used to assess the patients' conditions: (1) Swallowing function classification: A water swallowing test[16] was used to evaluate the swallowing function classification of the two groups before and after the intervention. The specific method was as follows: Patients drank 30 mL warm water and their swallowing condition was observed to evaluate the rehabilitation effect. Classification: Level 1 (5 points): Can successfully swallow water once within 5 s; level 2 (4 points): More than one attempt is needed to swallow the water, but there is no choking; level 3 (3 points): Water is swallowed at one time, but there is choking; level 4 (2 points): More than one attempt is needed to swallow the water and there is coughing; level 5 (1 point): Cannot swallow all of the water, and there is frequent coughing; (2) Swallowing function: The standardized swallowing assessment (SSA)[17] was used to evaluate the swallowing function of the two groups before and after the intervention. The examination steps were divided into three parts: Clinical examination, including consciousness, head and torso control, respiration, lip closure, soft palate movement, laryngeal function, pharyngeal reflex, and spontaneous cough, with a total score of 8–23 points; and patients were instructed to swallow 5 mL water three times to observe and evaluate whether there was swallowing movement, repeated swallowing, or wheezing during swallowing (total score: 5–11 points). If no abnormality was observed in the above operation, the patient was instructed to swallow 60 mL of water to evaluate whether they coughed during swallowing and the time required for swallowing (total score: 5–12 points). The total combined score for these three steps was 18–46 points. The swallowing function of patients was inversely proportional to the score; that is, the higher the score, the worse the function; (3) Negative emotions: Anxiety and depression were evaluated before and after the intervention. The former was evaluated using the self-rating anxiety scale (SAS)[18], with a full score and a critical value of 100 points and 50 points, respectively. The latter was assessed using the self-rating depression scale (SDS)[19]. The total possible score was 100 points, and the critical value was set at 53 points. The final score was proportional to the severity of anxiety and depression; (4) Quality of life: The Swallowing-Related Quality of Life questionnaire (SWAL-QOL)[20] was used to evaluate the quality of life of the two groups before and after the intervention. The scale assesses 11 dimensions, including eating, psychology, communication, and sleep, *via* a total of 44 items, each of which is rated using a five-point Likert scale, with a maximum total score of 220 points. The score is proportional to the quality of life; and (5) Occurrence of aspiration and aspiration pneumonia: Judged by history of aspiration; presence of purulent sputum or significantly increased sputum volume, wet rales, or lung consolidation signs, with body temperature > 38.5 °C. Pulmonary CT examination was used to confirm the occurrence of pneumonia.

Statistical analysis

Data were analyzed using IBM SPSS software (version 29.0). Frequency variables are expressed as *n* (%), and continuous variables are reported as the mean ± SD. Between group differences in these variables were tested using *t*-tests and χ^2 tests, respectively. Statistical significance was set at *P* < 0.05.

RESULTS

Classification of swallowing function

Pre-intervention, the coalition and regular groups showed no significant differences across the various baseline variables (*P* > 0.05). The number of cases of grade 1 swallowing function in the coalition group was higher than that in the regular group, and the number of cases of grade 5 swallowing function was lower in the coalition group than that in the regular group (*P* < 0.05; Table 2).

SSA score

Pre-intervention, the SSA ratings of the coalition and regular groups did not differ significantly (*P* > 0.05). Post-intervention, the SSA scores in both the coalition and regular groups decreased, and the reduction in the coalition group was significantly larger (*P* < 0.05; Table 3).

Negative emotion

Pre-intervention, the SAS and SDS scores of the coalition group were 54.02 ± 6.88 points and 55.29 ± 6.51 points, respectively, and those of the regular group were 54.22 ± 6.92 points and 55.04 ± 6.46 points, respectively. There were no

Table 2 Comparison of swallowing function classification between the two groups pre- and post-intervention, *n* (%)

Group	Level 1		Level 2		Level 3		Level 4		Level 5	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Coalition group (<i>n</i> = 45)	0 (0.00)	18 (40.00)	9 (20.00)	14 (31.11)	12 (26.67)	7 (15.56)	15 (33.33)	5 (11.11)	9 (20.00)	1 (2.22)
Regular group (<i>n</i> = 45)	0 (0.00)	8 (17.78)	10 (22.22)	11 (24.44)	11 (24.44)	10 (22.22)	16 (35.56)	9 (20.00)	8 (17.78)	7 (15.56)
χ^2	-	5.409	0.067	0.498	0.058	0.653	0.049	1.353	0.073	4.939
<i>P</i> value	-	0.020	0.796	0.480	0.809	0.419	0.824	0.245	0.788	0.026

-: Indicates no data.

Table 3 Comparison of standardized swallowing assessment scores between the two groups pre- and post-intervention

Group	Pre-intervention	Post-intervention
Coalition group (<i>n</i> = 45)	36.09 ± 4.75	22.76 ± 3.34 ^a
Regular group (<i>n</i> = 45)	35.93 ± 4.70	28.40 ± 4.11 ^a
<i>t</i>	0.156	-7.147
<i>P</i> value	0.876	< 0.001

^a*P* < 0.000001.

statistically significant differences between the two groups (*P* > 0.05). Post-intervention, the SAS and SDS scores of the coalition group were 40.67 ± 3.18 points and 41.80 ± 2.94 points, respectively, which were lower than those of the regular group at 44.22 ± 3.57 points and 45.09 ± 3.17 points, respectively (*P* < 0.05; **Figure 1**).

Quality of life

Pre-intervention, there was no significant difference in the total SWAL-QOL score or the scores of each dimension between the coalition and regular groups (*P* > 0.05). Post-intervention, the total SWAL-QOL score and the scores of each dimension in the coalition and regular groups increased; however, the increase in the coalition group was larger (*P* < 0.05; **Table 4**).

Occurrence of aspiration and aspiration pneumonia

During the intervention period, the total incidence of aspiration and aspiration pneumonia in the coalition group (4.44%) was lower than that in the control group (20.00%; *P* < 0.05; **Table 5**).

DISCUSSION

OD is a common complication of stroke. In such patients, the motor nerves of the mouth muscles, including the tongue, masticatory muscles, and throat muscles, are affected by stroke. Dysphagia occurs after the impairment of muscle motor function. Studies have found that dysphagia can lead to the occurrence of asphyxia and food aspiration in patients[5,21]. Long-term dysphagia can lead to poor nutritional status, increased tension and pessimism, and higher mortality rates among patients[6]. Previously, routine nursing interventions relied solely on swallowing training, and it was often difficult to achieve optimal results. According to recent systemic interventions and reviews, the main rehabilitation goal for dysphagia after stroke is to start directly from the pathological mechanism of swallowing to provide safe swallowing and adequate nutritional intake[22].

From the perspective of traditional Chinese medicine theory, dysphagia syndrome is characterized by phlegm and blood stasis and should be treated using the Jianpi Lishi Huoxue Huayu method[23]. Feng *et al*[24] showed that Tongyan spray treatment can quickly take effect and improve the clinical symptoms of patients with dysphagia after stroke. Clematis is a member of the Ranunculaceae family. Its rhizome is pungent, salty, and warm. It dispels wind, removes dampness, dredges collaterals, relieves pain, eliminates phlegm and water, and disperses accumulations. It is often used in the treatment of rheumatic arthralgia, limb numbness, tendon and vein contracture, flexion and extension limitations, as well as bone-choking throat[10]. Lee *et al*[25] found that clematis can enhance the excitability of the smooth muscle of the digestive tract by changing it from rhythmic to peristaltic contractions. Studies have shown that a root decoction of clematis can enhance the esophageal peristalsis rhythm and increase its frequency[26]. Combined with the above modern determination of pharmacological effects of clematis, it is reasonable to assume that clematis is indispensable in the process of improving dysphagia by Tongyan spray. At present, clematis is not widely used in clinical practice, and

Table 4 Comparison of quality-of-life between the two groups pre- and post-intervention

Group	Pre- and post-intervention	Coalition group (n = 45)	Regular group (n = 45)	t	P value
Psychological burden	Pre	2.29 ± 0.69	2.18 ± 0.68	0.765	0.447
	Post	3.49 ± 0.69 ^d	2.56 ± 0.78 ^a	5.972	< 0.001
Symptom frequency	Pre	42.49 ± 10.05	40.64 ± 7.52	0.986	0.327
	Post	49.71 ± 9.12 ^b	46.13 ± 5.99 ^b	2.200	0.030
Food choice	Pre	4.84 ± 1.58	4.78 ± 1.24	0.223	0.824
	Post	6.53 ± 1.22 ^d	5.78 ± 1.39 ^b	3.470	0.001
Feeding time	Pre	4.71 ± 1.32	5.16 ± 0.88	-1.876	0.064
	Post	7.09 ± 1.53 ^d	6.09 ± 1.06 ^c	3.594	0.001
Willingness to eat	Pre	4.58 ± 1.12	4.49 ± 1.04	0.391	0.697
	Post	6.80 ± 1.71 ^d	5.20 ± 1.22 ^a	5.106	< 0.001
Fear	Pre	9.76 ± 1.80	9.67 ± 1.92	0.227	0.821
	Post	11.49 ± 1.90 ^c	10.02 ± 1.63	3.927	< 0.001
Language communication	Pre	5.49 ± 1.65	5.80 ± 1.59	-0.912	0.364
	Post	7.64 ± 1.45 ^d	6.56 ± 1.27 ^a	3.790	< 0.001
Social function	Pre	11.71 ± 1.97	11.84 ± 1.82	-0.333	0.740
	Post	16.93 ± 2.09 ^d	12.93 ± 1.97 ^a	9.334	< 0.001
Mental health	Pre	12.00 ± 1.49	11.84 ± 1.61	0.475	0.636
	Post	16.60 ± 2.49 ^d	12.49 ± 2.12	8.848	< 0.001
Fatigued	Pre	8.13 ± 1.38	8.00 ± 1.48	0.443	0.659
	Post	10.84 ± 1.38 ^d	8.98 ± 1.27 ^a	6.674	< 0.001
Sleep	Pre	6.42 ± 1.41	6.49 ± 0.94	-0.264	0.792
	Post	8.36 ± 0.96 ^d	7.00 ± 1.21 ^a	5.906	< 0.001
SWAL-QOL total score	Pre	112.42 ± 10.61	110.89 ± 9.17	0.733	0.465
	Post	145.49 ± 9.48 ^d	123.33 ± 7.85 ^d	12.077	< 0.001

^aP < 0.05.^bP < 0.001.^cP < 0.0001.^dP < 0.00001.

SWAL-QOL: Swallowing-Related Quality of Life.

Table 5 Comparison of aspiration and aspiration pneumonia between the two groups, n (%)

Group	Aspiration	Aspiration pneumonia	Total incidence
Coalition group (n = 45)	1 (2.22)	1 (2.22)	2 (4.44)
Regular group (n = 45)	5 (11.11)	4 (8.89)	9 (20.00)
χ^2			5.057
P value			0.024

research on its active ingredients remains relatively superficial. To facilitate broader clinical utilization of clematis, intensified research and development efforts should be directed toward novel clematis-derived pharmaceuticals. Such initiatives would provide a stronger theoretical foundation, enabling more widespread therapeutic application of this plant.

Oral function training is a new swallowing rehabilitation method that can improve the excitability of the central nervous system. The lip muscle training device is placed behind the lip, and the sensory signal is transmitted to the brainstem and cerebral cortex by stimulating the oral intima to promote the formation of new conduction pathways for

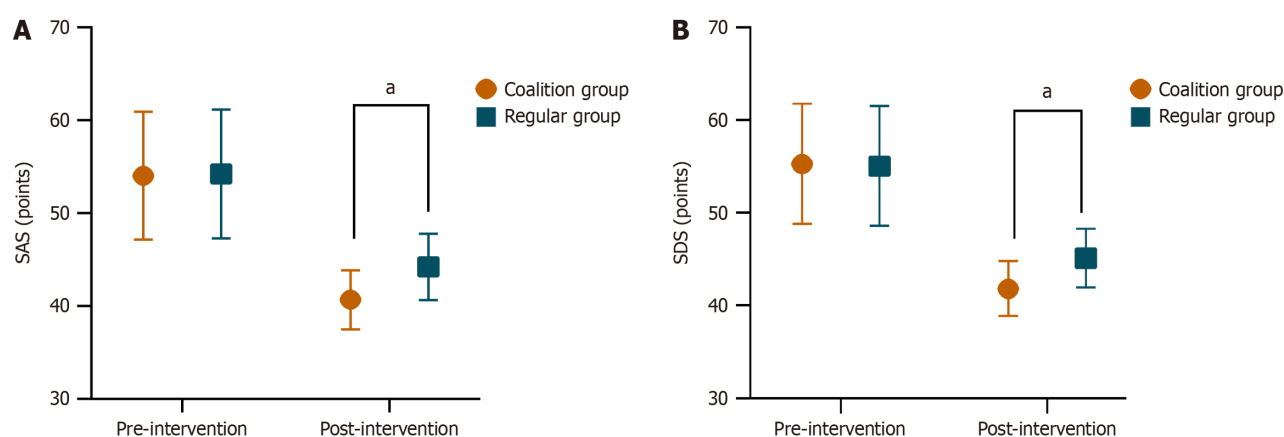


Figure 1 Comparison of psychological states between the groups before and after intervention. A: Self-rating anxiety scale score; B: Self-rating depression scale score. ^a $P < 0.00001$. SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

the related sensory-motor neurons and diseased nerve endings and to re-establish the motor reflex arc to promote the recovery of swallowing function in patients. Oral neuromuscular training stimulates swallowing function in the central nervous system, promotes swallowing-related motor neurons, and promotes the recovery of swallowing function in patients[27]. Hägglund *et al*[13] showed that oral neuromuscular training not only promotes the rehabilitation of swallowing function in older patients with dysphagia and improves malnutrition but also improves frailty and quality of life. At present, systemic rehabilitation training for patients with swallowing dysfunction can achieve some degree of positive effects; however, many patients in clinical practice have difficulty achieving the desired effect even after systemic rehabilitation treatment. Studies have shown that dysphagia is associated with depression[28]; thus, psychological problems in patients with dysphagia cannot be ignored. A study of rehabilitation nursing for patients with dysphagia showed that a psychological intervention based on routine swallowing therapy could significantly alleviate depression and improve swallowing function[29].

In this study, systemic intervention measures (aerosol inhalation of *Clematis chinensis* concentrated decoction combined with oral function training) and psychological interventions were applied to stroke patients with swallowing OD. After the intervention, the number of patients with grade 1 swallowing function in the coalition group was greater than that in the regular group, and the number of patients with grade 5 swallowing function was lower than that in the regular group. The SSA, SAS, and SDS scores of the coalition group were lower than those of the regular group. The total SWAL-QOL score and the scores for each dimension were higher in the coalition group than in the regular group. This shows that systemic intervention combined with psychological intervention can effectively improve the symptoms of dysphagia in stroke patients with OD, relieve negative emotions, and improve their quality of life.

The analysis of the pharmacological effects of aerosol inhalation of *Clematis chinensis* concentrated decoction suggests that it not only provides an effective treatment for use by doctors but also has a beneficial role in family rehabilitation nursing. Effective treatment promotes confidence in stroke patients and their families. At the same time, oral swallowing training can strengthen the coordination of muscles in the face, mouth, and tongue. It can also prevent atrophy of muscle groups related to swallowing movement, improve the flexibility of the swallowing reflex, enhance the swallowing function of patients, and improve their quality of life. In addition, psychological intervention and good nurse-patient trust relationships are integrated to encourage patients to gradually accept and adapt to the pathological state of swallowing dysfunction after stroke to alleviate the abnormal emotions caused by the sudden loss of function. Cooperation of family members helps patients establish confidence in overcoming the disease.

During the intervention period of this study, the total incidence of aspiration and aspiration pneumonia in the coalition group was 4.44%, which was lower than the 20.0% in the control group. These results indicate that systemic interventions combined with psychological interventions can reduce the incidence of aspiration and aspiration pneumonia in patients with stroke complicated by OD. The systemic intervention strengthened the patient's oral care, maintained their oral hygiene, and reduced their SSA score by reducing the aspiration of oral secretions caused by aspiration pneumonia[30]. Psychological intervention, doctor-nurse empathy, one-to-one guidance, and family members' participation in activities can help patients improve their compliance with safe eating, ensure the quality of health education, and reduce the occurrence of dietary accidents.

There are still some limitations to this study. First, the sample size is derived from a single source, and as our study has a retrospective design, it may introduce some selection bias. Second, the traditional Chinese medicine clematis was used for systematic intervention in this study. As the drug is not widely used for OD clinically and no in-depth research has been conducted on its active ingredients, the results may be affected to some extent. Therefore, future studies should focus on prospective, large-sample research and develop clematis-based drugs for further in-depth analysis.

CONCLUSION

A systemic intervention combined with psychological interventions can effectively improve the symptoms of dysphagia in stroke patients with OD, relieve negative emotions, improve quality of life, and reduce the occurrence of aspiration and aspiration pneumonia.

FOOTNOTES

Author contributions: Mao F, Song J, and Wang JD participated in the conception and design of the study; Mao F, Song J, and Wang JD provided administrative support for this research project; Huang JF, Chen J, and Chen D collected and analyzed the clinical data, and all authors approved the manuscript.

Supported by Qiqihar City Science and Technology Plan Joint Guidance Project, No. LSFSGG-2022085.

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

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

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

Data sharing statement: Datasets are available from the corresponding author at maof9929@qmu.edu.cn.

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S-Editor: Gong ZM

L-Editor: A

P-Editor: Zheng XM

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Clinical Trials Study

Application of psychological intervention in intensive care unit nursing for patients with severe acute pancreatitis

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade B, Grade B

P-Reviewer: Narod S, Canada; Pajic M, Australia

Received: April 3, 2024

Revised: May 7, 2024

Accepted: May 23, 2024

Published online: June 19, 2024

Processing time: 76 Days and 22.1 Hours



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Abstract

BACKGROUND

Severe acute pancreatitis (SAP) is a familiar critical disease in the intensive care unit (ICU) patients. Nursing staff are important spiritual pillars during the treatment of patients, and in addition to routine nursing, more attention needs be paid to the patient's psychological changes.

AIM

To investigate the effects of psychological intervention in ICU patients with SAP.

METHODS

One hundred ICU patients with SAP were hospitalized in the authors' hospital between 2020 and 2023 were selected, and divided into observation and control groups per the hospitalization order. The control and observation groups received routine nursing and psychological interventions, respectively. Two groups are being compared, using the Self-rating Anxiety Scale (SAS), Self-Determination Scale (SDS), Acute Physiology and Chronic Health Evaluation (APACHE) II, and 36-item Short Form Health Survey (SF-36) scores; nursing satisfaction of patients; ICU care duration; length of stay; hospitalization expenses; and the incidence of complications.

RESULTS

After nursing, the SDS, SAS, and APACHE II scores in the experimental group were significantly lower than in the control group ($P < 0.05$). The SF-36 scores in the observation group were significantly higher than those in the control group ($P < 0.05$). The nursing satisfaction of patients in the experimental group was 94.5%, considerably higher than that of 75.6% in the control group ($P < 0.05$). The ICU care duration, length of stay, and hospitalization expenses in the observation group were significantly lower than those in the control group, and the incidence of complications was lower ($P < 0.05$).

CONCLUSION

For patients with SAP, the implementation of standardized psychological intervention measures can effectively alleviate adverse psychological conditions.

Key Words: Severe acute pancreatitis; Intensive care unit nursing; Psychological intervention; Changes of psychological status; Short Form Health Survey

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Core Tip: Severe acute pancreatitis (SAP) is a dangerous acute clinical abdominal condition associated with high mortality. SAP treatment is usually performed in the closed environment of the intensive care unit, and an excellent psychological state helps exert the effect of various treatment methods and drugs to speed up disease recovery. We conducted a study on psychological interventions in 100 patients with SAP. This study found that psychological interventions effectively alleviated patients' anxiety, depression, and other adverse psychological conditions.

Citation: Huang CX, Xu XY, Gu DM, Xue HP. Application of psychological intervention in intensive care unit nursing for patients with severe acute pancreatitis. *World J Psychiatry* 2024; 14(6): 913-919

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/913.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.913>

INTRODUCTION

Acute pancreatitis is an inflammation of the pancreas caused by the activation of pancreatic enzymes, which leads to digestion and necrosis of the pancreatic tissue. Severe acute pancreatitis (SAP) is a serious acute clinical abdominal condition with a high mortality rate. SAP treatment is complex, and the case fatality rate is as high as 10%-25%[1]. Once multiple organ failure occurs, the case fatality rate can be as high as 80%[2,3]. Some patients who survive after active treatment can still have different degrees of pancreatic insufficiency and high treatment costs, and the family and society have brought a heavy burden. When SAP occurs, patients should be treated and nursed in the intensive care unit (ICU) immediately to ensure their safety[4,5].

The process of planning and gradually changing an object's psychological behaviours, personality traits, or psychological issues in order to move it towards the desired outcome under the direction of psychological theories is known as psychological intervention[6]. With the gradual development of modern nursing, people have gradually realized that considering only the physiological aspects of nursing is not enough. Nonetheless, they must also consider the relationship between health and disease, such as psychological and social factors[7]. With the extensive development of SAP surgical treatment in the ICU, most patients experience anxiety, fear, insomnia, irritability, depression, and other emotions during perioperative nursing, which negatively impact surgical treatment and rehabilitation. Targeted psychological nursing interventions have become an essential topic in surgical nursing and have received increasing clinical attention. Targeted psychological nursing intervention can alleviate patients' emotions and reduce the negative effects of surgical treatment and rehabilitation.

This study offers a fresh perspective on ICU nursing in SAP by examining the impact of psychosocial treatments in ICU care for SAP.

MATERIALS AND METHODS

Participants

Based on the sequence of hospitalisation, 100 SAP patients who were hospitalised to our hospital's ICU between January 2020 and December 2023 were chosen and split into observation and control groups. There were 45 cases in the control group, 25 men and 20 women, aged 25–72 years, with an average age of 44.64 ± 3.72 years. There were 55 cases in the observation group, including 33 men and 22 women, aged from 24 to 73 years old, with an average age of 45.46 ± 3.25 years.

Inclusion criteria: (1) According to the "Chinese guidelines for the management of acute pancreatitis (2021)" developed by the Pancreatic Diseases Group of the Gastroenterology Branch of the Chinese Medical Association, every patient satisfied the SAP diagnostic criteria[8]; (2) No history of mental disorders or psychiatric diseases; (3) Admitted to ICU; and (4) Patients and their families gave informed consent and signed.

Exclusion criteria: (1) Combined with severe liver, kidney, and other organ function abnormalities; (2) Comprehension and speech impairments; (3) Individuals with depression caused by primary depression or other diseases; and (4) Other reasons for dropping out of the study halfway.

Methods

Normal nursing care was provided to the control group, including assessing the patients' condition, vital sign support, strict observation, analgesic care, maintaining various pipes, recording fluid intake and outflow, and nutritional support. Based on the control group, the observation group underwent the following psychological intervention: (1) Cognitive psychological intervention: Most patients due to the lack of awareness of their disease, coupled with the postoperative ICU after seeing a variety of indwells on the body and unfamiliar with the surrounding instruments so that patients are prone to anxiety and fear. Furthermore, other psychological and severe cases may even develop mental disorders. Therefore, nursing staff needs to conduct health education for patients, introduce the etiology and possible complications of SAP, inform patients about the use and importance of the indwelling pipeline and the effect of treatment, eliminate patients' doubts, help them establish confidence in healing, and help improve patients' awareness of the self-protection pipeline, which is conducive to the improvement of treatment effect and prognosis; (2) Psychological support: After the patient is transferred to the ICU, the accompanying time of the family is limited, coupled with an unfamiliar hospital environment. Patients are prone to loneliness, resulting in depression, which has a specific impact on the development of nursing work. Nursing staff need to communicate with patients actively. Moreover, they should carefully observe changes in their mental state, master the psychological problems and needs of patients through communication, provide targeted psychological counseling, and meet the reasonable requirements of patients as far as possible. Simultaneously, encourage and comfort them, eliminate their negative emotions, and improve patient compliance to ensure the smooth progress of nursing work; and (3) Environmental management: First, the noisy environment will aggravate the anxiety and depression of patients. Therefore, the nursing staff first needs to ensure a quiet indoor and outdoor environment, adjust the volume of the monitoring instrument to a minimum, turn off the unused instrument in time, and prevent the nursing staff from talking and laughing loudly. Second, it is necessary to keep the indoor light soft, organize the items in time, and ensure that the indoor items are neatly placed. Furthermore, the preferred items should be placed near the patient according to their preferences to provide a comfortable and warm rest environment.

Evaluation index

Mental state before and after nursing was evaluated using the Self-rating Anxiety Scale (SAS)[9] and Self-Determination Scale (SDS)[10]. The twenty items on the SAS self-report scale address a range of anxiety symptoms, including physical and psychological symptoms. Higher scores indicate more severe symptoms. The SAS scores range from 20 to 80. Less than 50 points overall is considered normal; 50–59 represents mild anxiety, 60–69 represents moderate anxiety, while 69 or higher denotes severe anxiety. The SDS comprises 20 items that represent an individual's subjective emotions of depression. Each item is categorised into four grades based on the frequency of symptoms, with 10 positive and 10 reverse scores. The SDS standard score had a cut-off point of 53 points, with mild depression being defined as 53–62, moderate depression as 63–72, and severe depression as 73 or higher.

The Acute Physiology and Chronic Health Evaluation (APACHE) II score was used to evaluate symptom improvement before and after nursing[11]. The APACHE II comprises acute physiology, age, and chronic health evaluation. An APACHE II score of 71 is the theoretical maximum; the greater the score, the more severe the illness. The two groups' ICU monitoring duration, length of stay, and hospital costs were noted, and a statistical analysis was performed to determine the frequency of problems, which included sepsis, respiratory failure, heart failure, acute kidney failure, and gastrointestinal bleeding. The quality of life following nursing was assessed using the 36-item Short Form Health Survey (SF-36), which assessed physiological function, mental health, emotional role, physical pain, vitality, social capacity, and overall health score[12]. The standard formula is used to calculate the conversion score, so that each dimension can be converted into 0–100 points, and the conversion score of each dimension = $[(\text{actual score} - \text{lowest possible score}) / \text{general average possible score}] \times 100$.

Statistical methods

SPSS Windows software version 26.0 was used to analyze the data, and the mean \pm SD and n (%) were used to express the measurement and count data, respectively. Normal analysis and homogeneity test of variance were carried out on the measurement data. If the data followed normal distribution and the variance was homogeneous, t test (two-tailed) was carried out; otherwise, non-parametric test was carried out. The count data were analyzed by χ^2 tests, and $P < 0.05$ indicated that the difference was statistically significant.

Table 1 Comparison of mental state and severity of illness before and after nursing

Groups	n	SAS		t value	P value	SDS		t value	P value	APACHE II		t value	P value
		Before	After			Before	After			Before	After		
Observation group	55	45.67 ± 4.426	37.78 ± 6.525	7.439	< 0.001	58.89 ± 6.106	39.31 ± 3.620	20.458	< 0.001	38.05 ± 6.908	20.62 ± 1.958	18.010	< 0.001
Control subjects	45	45.73 ± 4.459	42.82 ± 4.207	3.186	0.002	60.16 ± 6.060	56.22 ± 7.856	2.659	0.009	38.29 ± 6.747	25.33 ± 1.871	12.412	< 0.001
t value		-0.048	-4.474			-1.034	-14.236			-0.171	-12.222		
P value		0.962	< 0.001			0.304	< 0.001			0.865	< 0.001		

SAS: Self-rating Anxiety Scale; SDS: Self-Determination Scale; APACHE: Acute Physiology and Chronic Health Evaluation.

RESULTS

Comparison of mental state and severity of illness before and after nursing

There were 55 patients in the observation group and 45 patients in the control group, of which 58 were men and 42 were women, with a mean age of 54.74 ± 12.955 years. There were no significant differences in the SDS, SAS, and APACHE II scores between the two groups at admission ($P > 0.05$). After nursing care, the scores of the two groups were significantly lower than those at admission. The SAS score of the observation was 37.78 ± 6.525 points, which was considerably lower than that of the control group (42.82 ± 4.207 points; $t = -4.474$, $P < 0.001$). The SDS score of the observation group was 39.31 ± 3.620 points, significantly lower than that of the control group (56.22 ± 7.856 points; $t = -14.236$, $P < 0.001$). The APACHE II score of the observation group was 20.62 ± 1.958 points, significantly lower than that of the control group (25.33 ± 1.871 points; $t = -12.222$, $P < 0.001$), and the difference between groups was statistically significant (Table 1).

Comparison of SF-36 scale scores before and after nursing intervention

Following nursing care, the observation group's SF-36 scores were significantly higher than the control group's for physical functioning, role-physical, bodily pain, vitality, social functioning, role-emotional, mental health, and general health ($P < 0.05$; Table 2).

Comparison of nursing satisfaction

The nursing satisfaction of patients in the experimental group was 94.5%, which was significantly higher than that in the control group (75.6%; $P < 0.05$; Table 3).

Comparison of hospitalization indexes

The ICU care duration, length of stay, and hospitalization expenses in the observation group were significantly lower than those in the control group, and the incidence of complications was lower ($P < 0.05$; Table 4).

Table 2 Comparison of 36-item Short Form Health Survey scale scores before and after nursing intervention (min, mean \pm SD)

Groups	<i>n</i>	PF	RP	BP	GH	VT	SF	RE	MH	Total
Observation group	55	45.36 \pm 3.658	62.65 \pm 4.213	58.07 \pm 6.315	58.75 \pm 6.210	60.51 \pm 6.076	59.18 \pm 4.643	57.38 \pm 5.438	57.36 \pm 5.923	58.33 \pm 6.209
Control subjects	45	40.96 \pm 3.398	47.53 \pm 4.429	49.93 \pm 2.871	52.58 \pm 2.241	53.22 \pm 3.147	50.33 \pm 2.714	51.58 \pm 2.943	52.84 \pm 3.247	53.18 \pm 3.291
<i>t</i> value	-	6.188	17.448	7.991	6.329	7.281	11.296	6.427	4.583	5.041
<i>P</i> value	-	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

PF: Physical functioning; RP: Role-physical; BP: Bodily pain; GH: General health; VT: Vitality; SF: Social functioning; RE: Role-emotional; MH: Mental health.

Table 3 Comparison of nursing satisfaction between two groups

Groups	<i>n</i>	Satisfaction	More satisfactory	Dissatisfaction	Overall satisfaction, <i>n</i> (%)
Observation group	55	38	14	3	52 (94.5)
Control subjects	45	21	13	11	34 (75.6)
χ^2					8.593
<i>P</i> value					0.014

Table 4 Comparison of hospitalization indexes between the two groups

Groups	<i>n</i>	ICU care duration (day)	Length of stay (day)	Hospitalization expenses (ten thousand yuan)	Occurrence of complications, <i>n</i> (%)
Observation group	55	2.16 \pm 0.834	18.27 \pm 1.661	7.90 \pm 0.700	4 (7.3)
Control subjects	45	4.11 \pm 1.465	22.58 \pm 3.130	10.46 \pm 2.115	11 (24.4)
<i>t</i> / χ^2	-	-8.349	-8.805	-8.431	5.724
<i>P</i> value	-	< 0.001	< 0.001	< 0.001	0.024

DISCUSSION

At least two of the following three requirements should be satisfied for a SAP diagnosis: (1) Upper abdominal pain, increased serum amylase level by more than three times; (2) Acute pancreatitis on computed tomography or magnetic resonance imaging, accompanied by extensive peripancreatic exudation or pancreatic necrosis, or pancreatic abscess; and (3) Organ failure[13,14]. SAP belongs to the category of acute severe diseases; its condition is critical, its prognosis is poor, and it directly threatens the safety of patients. Even after being out of danger, there may still be different degrees of pancreatic function problems that can lead to fever, abdominal pain, shock, and other symptoms in patients, thus seriously affecting their quality of life.

Since the treatment of SAP is primarily conducted in the closed environment of the ICU, patients suffer apparent physical pain and face a series of psychological stress reactions, resulting in psychological abnormalities and disorders that seriously affect treatment and prognosis. As the only spiritual pillar of patients, nursing staff play a vital role in creating and maintaining a good mental state. An excellent psychological state helps to exert the effects of various treatments and drugs but also helps to enhance patients' enthusiasm for treatment, take the initiative to participate in self-care, and speed up the recovery of the disease. Therefore, in ICU care, in addition to routine condition monitoring, medication guidance, pipeline care, and health education, attention should be paid to the psychological state of patients and the timely detection of their adverse emotions through reasonable psychological counseling methods to help patients establish confidence in rehabilitation, better cooperate with nursing work, and promote the improvement of nursing quality.

In the process of psychological intervention, nursing staff should observe and communicate with patients promptly to obtain recognition and support for patients in the treatment process. In this study, psychological intervention was added to the experimental group of patients, and the results showed that there were no statistically significant differences in the SDS, SAS, and APACHE II scores between the two groups before nursing ($P > 0.05$). Nevertheless, they were significantly reduced after nursing ($P < 0.05$). Following nursing care, the experimental group's SDS, SAS, and APACHE II scores were considerably lower than those of the control group ($P < 0.05$), in line with the majority of the experimental findings[15,16].

After receiving nursing care, the observation group's SF-36 score was considerably greater than that of the control group ($P < 0.05$). Additionally, the experimental group's patient nursing satisfaction rate was 94.5%, significantly higher than the control group's 75.6%, and the difference was statistically significant ($P < 0.05$) [17,18]. These results indicate that psychological interventions can significantly alleviate patients' anxiety and depression and improve nursing satisfaction. The results of hospitalization indicators showed that ICU care duration, length of stay, as well as hospitalisation expenses were considerably lower in the observation group compared to the control group ($P < 0.05$). There was also a significant reduction in the incidence of complications. It has been thoroughly proven that the application effect of psychological interventions in ICU nursing for SAP is exact. This can better help patients adjust their mentality, actively cooperate with treatment, promote early remission of the disease, improve the quality of life, and reduce the burden of life. It is worthy of clinical promotion and use.

However, there are some limitations to this study. First of all, due to various reasons, the survey sample is limited to our hospital, and the sample size is relatively small. In addition, the quality of surveys and data analyses involving only patients in the region cannot be fully guaranteed. Therefore, the findings are representative of this region only, and further studies with a wider and diverse population range are needed if they are to be generalized to other regions.

CONCLUSION

In conclusion, for patients with SAP, standardized psychological intervention measures can effectively alleviate adverse psychological conditions, such as anxiety and depression. Furthermore, they accelerate physical rehabilitation by improving treatment and nursing compliance, which has significant clinical application value.

FOOTNOTES

Author contributions: Huang CX and Xu XY designed the research study; Huang CX, Xu XY, Gu DM, and Xue HP performed the research; Huang CX, Xu XY, Gu DM, and Xue HP contributed new reagents and analytical tools; Huang CX and Xu XY analyzed the data and wrote the manuscript; all authors have read and approved the final version of the manuscript. Huang CX and Xu XY, as co-authors, played an important role in research design by jointly conceptualizing the overall framework and plan of the study; Gu DM and Xue HP, as co-corresponding authors, provided important guidance and support for the progress of the study, contributions of new reagents and analytical tools, as well as data analysis and manuscript writing; Throughout the entire research process, Huang CX, Xu XY, Gu DM, and Xue HP worked closely together to leverage their professional strengths and jointly promote the smooth progress of the research; Their joint efforts and contributions have enabled the success of this research and provided valuable references for further research in the field.

Institutional review board statement: The study was reviewed and approved by the Science and Research Office of Affiliated Hospital of Nantong University.

Clinical trial registration statement: The study was registered at the Clinical Trial Center with registration number: researchregistry10268.

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

Conflict-of-interest statement: Dr. Gu has nothing to disclose.

Data sharing statement: No additional data are available.

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

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S-Editor: Lin C

L-Editor: A

P-Editor: Che XX

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Observational Study

Change in self-image pressure level before and after autologous fat breast augmentation and its effect on social adaptability

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C, Grade C

Novelty: Grade B, Grade C

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade B, Grade B

P-Reviewer: Lindqvist D, Sweden; Perina A, Czech Republic

Received: February 21, 2024

Revised: April 15, 2024

Accepted: May 7, 2024

Published online: June 19, 2024

Processing time: 119 Days and 3.2 Hours



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Abstract

BACKGROUND

There is an increasingly strong demand for appearance and physical beauty in social life, marriage, and other aspects with the development of society and the improvement of material living standards. An increasing number of people have improved their appearance and physical shape through aesthetic plastic surgery. The female breast plays a significant role in physical beauty, and droopy or atrophied breasts can frequently lead to psychological inferiority and lack of confidence in women. This, in turn, can affect their mental health and quality of life.

AIM

To analyze preoperative and postoperative self-image pressure-level changes of autologous fat breast augmentation patients and their impact on social adaptability.

METHODS

We selected 160 patients who underwent autologous fat breast augmentation at the First Affiliated Hospital of Xinxiang Medical University from January 2020 to December 2022 using random sampling method. The general information, self-image pressure level, and social adaptability of the patients were investigated using a basic information survey, body image self-assessment scale, and social adaptability scale. The self-image pressure-level changes and their effects on the social adaptability of patients before and after autologous fat breast augmentation were analyzed.

RESULTS

We collected 142 valid questionnaires. The single-factor analysis results showed

no statistically significant difference in the self-image pressure level and social adaptability score of patients with different ages, marital status, and monthly income. However, there were significant differences in social adaptability among patients with different education levels and employment statuses. The correlation analysis results revealed a significant correlation between the self-image pressure level and social adaptability score before and after surgery. Multiple factors analysis results showed that the degree of concern caused by appearance in self-image pressure, the degree of possible behavioral intervention, the related distress caused by body image, and the influence of body image on social life influenced the social adaptability of autologous fat breast augmentation patients.

CONCLUSION

The self-image pressure on autologous fat breast augmentation patients is inversely proportional to their social adaptability.

Key Words: Autologous fat breast augmentation surgery; Self-image stress level; Social adaptability; Analysis of correlation; Structural equation model

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Core Tip: We selected a random clinical sample for a questionnaire survey of patients undergoing autologous fat breast augmentation. A body image disturbance questionnaire and Self-report Psychosocial Adjustment to Illness Scale were used to evaluate the self-image stress level and social adaptability of the patients, and a validity test of the questionnaire showed that it had high reliability. The results of the questionnaire showed that the preoperative self-image stress level and social adaptability score of the patients were generally high, and there was a correlation between the two. The self-image pressure was relieved, and the social maladjustment was significantly reduced.

Citation: Li J, Wang HM, Jiang Y, Liu ZN, He BH. Change in self-image pressure level before and after autologous fat breast augmentation and its effect on social adaptability. *World J Psychiatry* 2024; 14(6): 920-929

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/920.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.920>

INTRODUCTION

With the development of society and the improvement of material living standards, individuals have increasingly strong demands for appearance and physical beauty in social life, marriage, and other aspects. An increasing number of people are improving their appearance and physical shape through aesthetic plastic surgery[1]. The breast is a sign of female physical beauty; droopy or atrophied breasts can often lead to feelings of psychological inferiority and lack of confidence, which may adversely affect mental health and quality of life. Breast augmentation surgery is a common practice in plastic and aesthetic surgery. An increasing number of women are seeking breast augmentation surgery because of breast shape problems to improve their self-confidence and meet their social and work needs[2]. As a relatively safe and natural plastic method, autologous fat breast augmentation is favored by many women who pursue a beautiful physique[3]. However, existing studies have shown that approximately 52% of patients undergoing plastic surgery have a specific degree of psychological disorder[4]. With the continuous evolution of appearance anxiety and aesthetic standards, the expectations for plastic surgery are no longer limited to external aesthetic feelings, and the popularity of aesthetic plastic surgery is accompanied by a series of social and psychological problems[5,6]. Changes in the expectations, self-perception, social adaptability, and other aspects of patients are complex and worthy of in-depth research[7].

Autologous fat breast augmentation has become a prominent cosmetic procedure that reflects the evolving landscape of aesthetic enhancements. This study fills a gap in the literature by focusing on the nuanced psychological dynamics associated with this surgery. Studies have shown that the reduction of self-image stress levels can effectively reduce emotional distress and improve interpersonal skills[8,9]. Therefore, this study mainly analyzes the self-image pressure of autologous fat breast augmentation patients and the relationship between social adaptation and plastic surgery for women to provide a more comprehensive assessment framework and personalized service for medical plastic surgery.

MATERIALS AND METHODS

General information

We selected 160 patients who underwent autologous fat breast augmentation at the First Affiliated Hospital of Xinxiang Medical University Hospital from January 2020 to December 2022 as research participants using the random sampling method. The inclusion criteria were as follows: (1) Voluntarily accepted autologous fat augmentation; (2) Above

elementary school culture level and correctly understood and completed the questionnaire; and (3) Good language skills. The exclusion criteria included: (1) Age: ≥ 45 years old; (2) Patients with post-breast surgery pain and areola bag piece swelling; (3) Patients with malignant tumors, mental diseases, and other diseases that seriously affect the quality of life. Informed consent was obtained from all the patients.

Questionnaire survey

Basic information questionnaire: The basic information questionnaire was designed by the members of the investigation team, and the main statistics were the demographic data of the patients. The data included age, marital status (married with children, unmarried with children, unmarried without children, and married without children), education (primary school, junior high school, senior high school, college, bachelor's degree, or above), and monthly income (less than 3500 yuan/month, 3500-8000 yuan/month, and more than 8000 yuan/month), employment situation (employed, unemployed, seeking employment).

Body image disturbance questionnaire: Body image disturbance questionnaire (BIDQ) is a self-report evaluation method that includes seven problems; recent reports have verified the effectiveness of the BIDQ. The BIDQ assesses the extent to which participants have concerns about their appearance and the resulting anxiety and impairment of daily life functions. The BIDQ targets healthy individuals.

Self-report Psychosocial Adjustment to Illness Scale: Self-report Psychosocial Adjustment to Illness Scale (PAIS-SR) is mainly used to assess the psychological and social adjustment of patients. It includes seven dimensions (health care, work ability, family relationship, sexual life, communication, entertainment, and psychological status) with a total of 46 items. The internal consistency was 0.81, and the inter-rater reliability was 0.86. Each item score of the PAIS-SR ranges from 0 to 3, and the total score ranges from 0 to 138. Higher scores indicate more social adjustment problems.

Survey methods

General information, BIDQ, and PAIS-SR were completed at the time of the visit. The questionnaire survey was conducted one-on-one, with voluntary participation as the principle. Six months post-operation, the patients were followed up and completed the BIDQ and PAIS-SR again.

Statistical analysis

When the data were normally distributed, the standard deviation of the mean \pm SD was used to represent the measurement data, and the median (lower quartile, upper quartile) was used to represent the non-normally distributed data. *T*-test was used for single-factor analysis, and the homogeneity of variance test was used for multi-group data comparison. Percentage (%) represented count data, and the χ^2 test was used for univariate analysis. Cronbach's coefficient reliability test was used to analyze the internal consistency of each dimension of the scale. A hypothesis was proposed to establish a structural equation model of the effect of changes in the self-image pressure levels of patients on their social adaptability. The model fitness was tested, and the null hypothesis of a path coefficient greater than zero was established. The Pearson correlation analysis was used for data conforming to a normal distribution, and the Spearman correlation analysis was used for data not conforming to a normal distribution. Linear regression analysis was used for the multivariate analysis. All patients were treated with $P < 0.05$, indicating that the difference was statistically significant.

RESULTS

Autologous fat breast augmentation patients' questionnaire results

We distributed 160 questionnaires, and 142 valid questionnaires were collected, with an effective recovery rate of 88.75%. Analysis of preoperative PAIS-SR and BIDQ results across patient demographics revealed no statistically significant differences in self-image stress levels and social adaptation scores among different age groups, marital statuses, and monthly incomes ($P > 0.05$). However, significant differences were observed in social adaptability and self-image pressure among patients with varying education levels and employment statuses ($P < 0.05$), as shown in Table 1.

PAIS-SR and BIDQ reliability analysis

The factors of the self-image pressure and social adaptability of patients were measured using a questionnaire, and the data quality of the patient questionnaire measurement results was tested to ensure the significance of the subsequent analysis. Cronbach's coefficient reliability test results showed that the internal consistency of the BIDQ, PAIS-SR, and their various dimensions had high credibility, as shown in Table 2.

Self-image stress level and social adaptability structural equation model

Based on demographic data analysis, patients' employment status was categorized into employed and unemployed. Subsequently, the following hypotheses were formulated: (1) Self-image stress levels have a positive impact on the social adaptability of patients on the job. A structural equation model was established and the χ^2 freedom ratio of the model was 1.323, indicating a good fit; and (2) The self-image stress level of unemployed patients has a positive impact on their social resilience. A structural equation model was established and the χ^2 freedom ratio of the model was 1.207, indicating a good fit. According to the path coefficient results of structural equation model, the BIDQ scale for employed patients has a standard path coefficient of $0.81 > 0$ for PAIS-SR quantity, and the BIDQ scale for unemployed patients has a

Table 1 Self-report Psychosocial Adjustment to Illness Scale score of patients in various demographic data (mean \pm SD)

Basic data		<i>n</i> (%)	Preoperative PAIS-SR	<i>F</i>	<i>P</i> value	Preoperative BIDQ	<i>F</i>	<i>P</i> value
Age (yr)	18-24	24 (16.90)	56.67 \pm 4.37	0.750	0.526	31.00 \pm 7.40	0.255	0.858
	25-31	83 (58.45)	58.15 \pm 4.29			30.81 \pm 7.33		
	32-38	30 (21.13)	56.63 \pm 6.24			31.26 \pm 7.82		
	≥ 39	5 (3.52)	56.33 \pm 3.51			33.33 \pm 8.14		
Marital status	Married childless	38 (26.76)	57.58 \pm 3.74	1.622	0.190	31.92 \pm 8.05	1.813	0.151
	Unmarried childless	31 (21.83)	59.26 \pm 5.24			27.58 \pm 7.78		
	Married with child	57 (40.14)	56.39 \pm 5.14			31.08 \pm 6.24		
	Married with children	16 (11.27)	58.10 \pm 3.84			33.20 \pm 7.83		
Degree of education	Primary and junior high schools	29 (20.42)	58.83 \pm 4.55	19.455	< 0.001	34.61 \pm 5.34	2.199	0.094
	High school	35 (24.65)	57.50 \pm 5.04			30.48 \pm 6.69		
	Specialty	40 (28.17)	56.36 \pm 5.24			29.50 \pm 6.41		
	Bachelor's degree or above	38 (26.76)	55.38 \pm 4.13			29.46 \pm 5.78		
Monthly income (yuan)	≤ 3500	14 (9.86)	59.56 \pm 6.77	1.440	0.243	29.78 \pm 10.32	0.203	0.817
	3500-8000	77 (54.22)	56.86 \pm 4.48			31.23 \pm 7.00		
	≥ 8000	51 (35.92)	57.94 \pm 4.42			30.44 \pm 7.19		
Employment situation	On guard	91 (64.08)	59.46 \pm 6.03	6.489	< 0.001	30.86 \pm 5.73	3.666	< 0.001
	Unemployment (including unemployment)	51 (35.92)	53.10 \pm 4.01			34.67 \pm 5.12		

PAIS-SR: Self-report Psychosocial Adjustment to Illness Scale; BIDQ: Body image disturbance questionnaire.

standard path coefficient of $0.78 > 0$ for PAIS-SR quantity, both of which indicate that the hypothesis is valid. Therefore, self-image stress level has a positive impact on social adaptability (Figure 1).

Correlation between the BIDQ and PAIS-SR before and after surgery

The BIDQ preoperative score of 142 patients was 30.80 ± 7.37 , and the postoperative score was 26.33 ± 6.79 ($P < 0.05$). The PAIS-SR score was 57.46 ± 8.51 before operation and 54.4 ± 8.13 after operation ($P < 0.05$). The postoperative self-image pressure of the patients decreased significantly, and the social adaptability significantly increased, as shown in Table 3.

The score of each dimension of the BIDQ was 5.32 ± 1.70 before the operation and 4.67 ± 1.34 after the operation. BIDQ2 was the degree of behavioral interventions, which was 4.97 ± 1.55 before the operation and 4.07 ± 1.29 after the operation. BIDQ3 represented the body image caused by problems before the operation (3.68 ± 1.18) and after the operation (3.11 ± 1.09). BIDQ4 represented social problems caused by the body image before the operation [3.00 ($2.00, 4.00$)] and after the operation [3.00 ($2.00, 4.00$)]. BIDQ5 represented the impact of body image on social life before the operation (4.60 ± 1.27) and after the operation (4.30 ± 1.25). The effect of body image on other role functions in the BIDQ6 score was 3.00 ($2.00, 4.00$) before the operation and 3.00 ($2.00, 4.00$) after the operation. BIDQ7 represented body image caused by avoidance behavior score before the operation [2.00 ($1.00, 3.00$)] and after the operation [2.00 ($1.00, 3.00$)]. The preoperative and postoperative scores of each BIDQ dimension and PAIS-SR showed that the self-image stress levels of the patients were significantly related to social adaptability problems. The higher the stress levels in patients, the more the social adaptability problems, as shown in Tables 4 and 5.

Table 2 Body image disturbance questionnaire and Self-report Psychosocial Adjustment to Illness Scale reliability analysis

Variables of interest		Cronbach's coefficient	Number of terms
Scale		0.883	7
PAIS-SR scale	Hygiene and health	0.837	7
	Ability to work	0.829	8
	Family situation	0.842	7
	Sexual ability	0.898	4
	Situation of communication	0.865	5
	The entertainment situation	0.813	6
	BIDQ psychological status	0.821	7
	Summary table	0.861	44

PAIS-SR: Self-report Psychosocial Adjustment to Illness Scale; BIDQ: Body image disturbance questionnaire.

Table 3 Patients with body image disturbance questionnaire and Self-report Psychosocial Adjustment to Illness Scale scores before and after surgery

	Before surgery	After surgery	<i>t</i>	<i>P</i> value
Total BIDQ score	30.80 ± 7.37	26.33 ± 6.79	4.209	< 0.001
Total PAIS-SR score	57.46 ± 8.51	54.4 ± 8.13	2.450	0.015

PAIS-SR: Self-report Psychosocial Adjustment to Illness Scale; BIDQ: Body image disturbance questionnaire.

Table 4 Correlation between the scores of body image disturbance questionnaire dimensions and Self-report Psychosocial Adjustment to Illness Scale scores of patients before surgery

Variables of interest	<i>r</i>	<i>P</i> value
Total BIDQ score	0.773	< 0.001
BIDQ1 appearance caused attention	0.848	< 0.001
The extent to which behavioral interventions may be undertaken in BIDQ2	0.727	< 0.001
BIDQ3 body image-related distress	0.775	< 0.001
BIDQ4 social issues caused by body image	0.850	< 0.001
BIDQ5 body image's impact on social life	0.791	< 0.001
Effect of body image on other role functioning in BIDQ6	0.765	< 0.001
BIDQ7 avoidance behaviors due to body image	0.645	< 0.001

PAIS-SR: Self-report Psychosocial Adjustment to Illness Scale; BIDQ: Body image disturbance questionnaire.

Multivariate analysis of the preoperative and postoperative PAIS-SR scores

Multiple regression analysis was performed with each dimension of the BIDQ scale as the independent variable and the PAIS-SR score as the dependent variable. The preoperative results showed that the adjusted $R^2 = 0.594$, $F = 207.244$, and $P < 0.001$; thus, the model was successfully established. Among them, the degree of concern caused by appearance in self-image pressure, the degree of possible behavioral intervention, the related distress caused by body image, and the influence of body image on social life were significantly positive predictors of social adaptability. Postoperative results showed that the adjusted $R^2 = 0.695$, $F = 46.909$, and $P < 0.001$; thus, the model was successfully established. The degree of concern caused by appearance, the degree of possible behavioral intervention, social problems caused by body image, and the influence of avoidance behavior caused by body image on postoperative self-image pressure significantly and positively predicted the level of the social adaptability of patients. The results are presented in Tables 6 and 7.

Table 5 Correlation between the scores of body image disturbance questionnaire dimensions and self-report psychosocial adjustment to illness scale scores in postoperative patients

Variables of interest	<i>r</i>	<i>P</i> value
BIDQ1 appearance caused attention	0.714	< 0.001
The extent to which behavioral interventions may be undertaken in BIDQ2	0.663	< 0.001
BIDQ3 body image-related distress	0.652	< 0.001
BIDQ4 social issues caused by body image	0.639	< 0.001
BIDQ5 body image's impact on social life	0.703	< 0.001
Effect of body image on other role functioning in BIDQ6	0.685	< 0.001
BIDQ7 avoidance behaviors due to body image	0.348	< 0.001
BIDQ1 appearance caused attention	0.401	< 0.001

BIDQ: Body image disturbance questionnaire.

Table 6 Multivariate analysis of preoperative Self-report Psychosocial Adjustment to Illness Scale scores

Independent variable	<i>b</i>	<i>Sb</i>	<i>b'</i>	<i>t</i>	<i>P</i> value
Degree of concern caused by the appearance in BIDQ1	1.784	0.660	0.249	2.704	0.008
The extent to which behavioral interventions may be undertaken in BIDQ2	2.282	0.646	0.245	3.531	0.001
BIDQ3 body image-related distress	1.882	0.71	0.202	2.651	0.009
BIDQ4 social issues caused by body image	1.161	0.721	0.114	1.612	0.109
BIDQ5 body image's impact on social life	1.786	0.534	0.288	3.346	0.001
Effect of body image on other role functioning in BIDQ6	0.679	0.598	0.083	1.135	0.259
BIDQ7 avoidance behaviors due to body image	0.386	0.427	0.057	0.903	0.368
Total BIDQ score	1.153	0.080	0.773	14.396	< 0.001

BIDQ: Body image disturbance questionnaire.

Table 7 Postoperatively, psychosocial adjustment to illness scale-multiple factors analysis of the self-report score

Independent variable	<i>b</i>	<i>Sb</i>	<i>b'</i>	<i>t</i>	<i>P</i> value
Degree of concern caused by the appearance in BIDQ1	1.308	0.545	0.185	2.399	0.018
The extent to which behavioral interventions may be undertaken in BIDQ2	1.185	0.438	0.162	2.707	0.008
BIDQ3 body image-related distress	0.979	0.548	0.113	1.785	0.076
BIDQ4 social issues caused by body image	2.155	0.439	0.344	4.908	< 0.001
BIDQ5 body image's impact on social life	0.984	0.528	0.131	1.863	0.065
Effect of body image on other role functioning in BIDQ6	0.279	0.372	0.041	0.751	0.454
BIDQ7 avoidance behaviors due to body image	0.698	0.325	0.118	2.148	0.034
Total BIDQ score	2.155	0.439	1.552	4.908	< 0.001

BIDQ: Body image disturbance questionnaire.

DISCUSSION

Cosmetic and plastic surgery are increasingly popular in contemporary society, and the development of social media gives the appearance a more significant role in social interaction. Individuals pay more attention to body image in terms of social interaction, marriage, and other aspects[10-13]. Autologous fat breast augmentation is becoming a popular

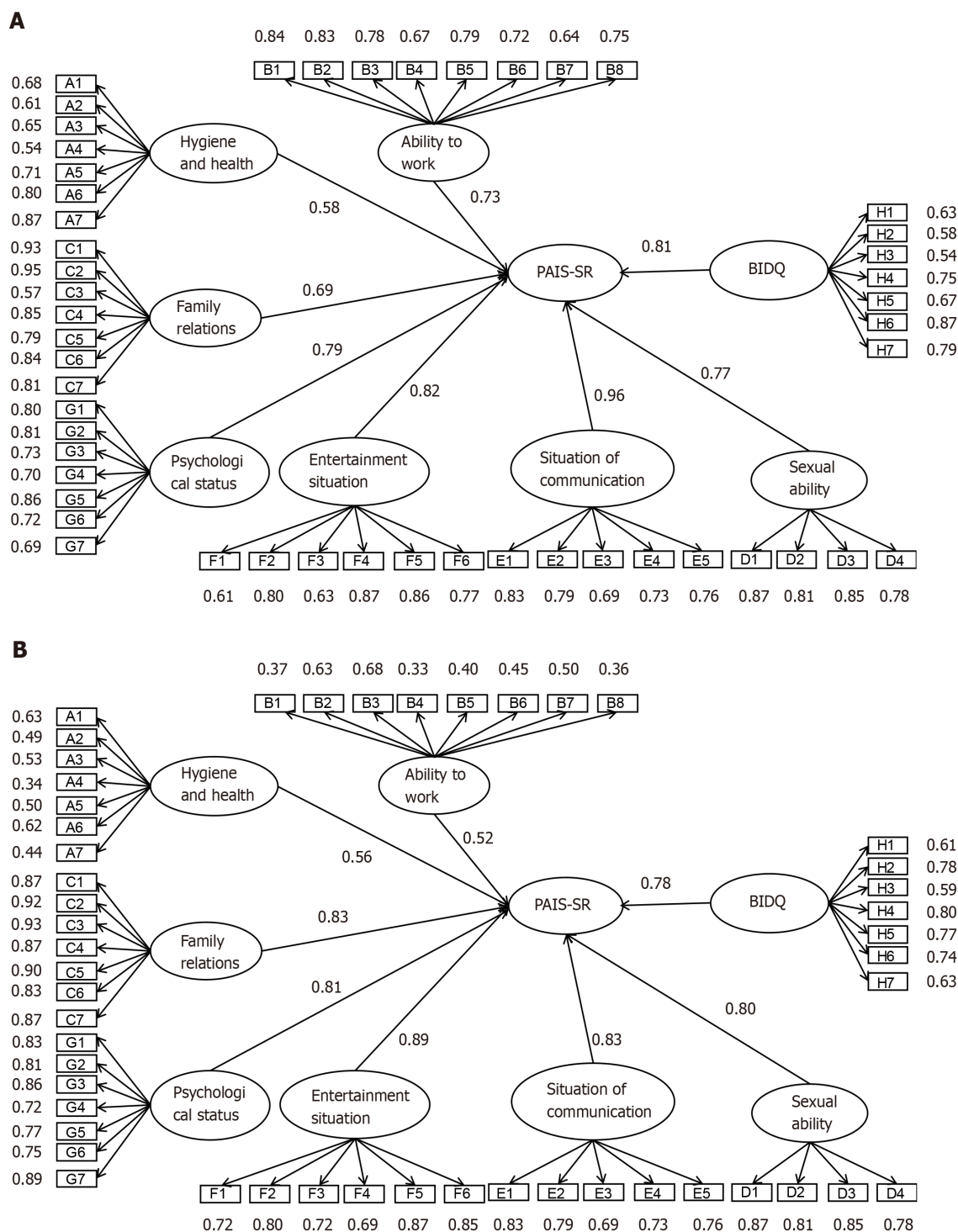


Figure 1 Self-image stress level impact on the social adaptability. A: Structural equation model of the effect of self-image stress level on the social resilience of employed patients; B: Structural equation model of the influence of self-image stress level on the social resilience of unemployed patients. A1-A7 represent topics 1-7 in the dimension of health care, respectively; B1-B8 represent questions 1-8 in the dimension of working ability, respectively; C1-C7 represent questions 1-7 in the dimension of family relationship, respectively; D1-D4 refers to questions 1-4 in the sexual ability dimension, respectively; E1-E5 indicates topics 1-5 in the communication dimension, respectively. F1-F6: represent topics 1-6 in the entertainment dimension, respectively; G1-G7 represent questions 1-7 in the dimension of psychological status, respectively. H1-H7: H1 represents the degree of concern caused by appearance; H2 represents the possible degree of behavioral intervention; H3 represents body image-related distress; H4 represents social and occupational problems caused by body image; H5 represents the impact of body image on social life; H6 represents the impact of body image on learning, work, or other role functions; H7 represents body image-induced avoidance behavior. PAIS-SR: Self-report Psychosocial Adjustment to Illness Scale; BIDQ: Body image disturbance questionnaire.

choice for the pursuit of beauty by females; cosmetic surgery is not only a physical change but is also more involved in the psychological state and social adaptation of the patients[14,15]. Therefore, this study focused on patients undergoing autologous fat breast augmentation surgery, with an in-depth investigation of self-image changes in stress levels before and after surgery and the relationship with social adaptability.

In this study, according to the results for preoperative autologous fat breast augmentation patients, the self-image stress level is high. This may be because society's aesthetic standards for women's body beauty have been changing, and patients have specific stereotypes about their image and chest fullness; drooping and shrinking breasts cause psychological inferiority[16-19]. Patients may be affected by media, social networks, and other aspects, and they may have experienced excessive pressure on their chest shape[20]. The preoperative social adaptability scale score of the patients was high, indicating preoperative social adaptability problems.

This study compared the social adaptability of different populations. Significant differences existed among the different cultural degrees of patients' social adaptability, possibly because the higher level of education and individual cognitive levels were positively related. A high degree of education indicates that the individual can analyze and solve difficulties and adapt to the new environment; further, they can cope with stress and have emotion management ability, which can help maintain a good psychological state and improve social adaptability[21,22]. In addition, there are significant differences in social adaptability and self-image stress levels between employed and unemployed patients. Unemployed patients may lack social support and recognition, prompting them to prioritize external images to obtain self-esteem and recognition. The results of structural equation model validated the theoretical hypothesis that self-image stress has a positive impact on social resilience in both employed and unemployed patients. Notably, family relationship factors have a greater impact on the social resilience of unemployed patients compared to unemployed ones. Unemployed patients may rely more heavily on family members as their main social support system, and the influence of family relationship on their social resilience and mental health may be more significant. Comparing the levels of self-image pressure and social adaptability before and after surgery revealed a significant reduction in overall postoperative self-image pressure and social maladjustment problems among patients. Compared with the preoperative self-image stress level and level of social adaptability of patients, the postoperative self-image pressure level was significantly reduced, thereby reducing social maladjustment problems. In this study, the total score and all dimensions of the self-image pressure level of patients were positively correlated with their social adaptation level; that is, the higher the self-image pressure level, the higher the social adaptation score, and the more the social maladjustment problems. Multiple factors analysis preoperative results showed that the adjusted R^2 was 0.594, showing that the preoperative BIDQ scale explained the 59.4% change in the PAIS-SR scale. Postoperative results showed that the adjusted R^2 was 0.695, showing that the postoperative BIDQ scale explained the 69.5% change in the PAIS-SR scale. The results of the study suggested that the degree of concern caused by the appearance of patients on the BIDQ scale, the degree of possible behavioral intervention, the related distress caused by body image, the influence of body image on social life, and the avoidance behavior caused by body image were closely related to the social maladjustment of patients. On the one hand, if too much attention is paid to the appearance of the patient, it may lead to social anxiety. For patients who experience low self-esteem and anxiety because of their body image, it may be difficult to show good adaptability in social occasions[23,24]. On the other hand, for patients who pay too much attention to their appearance, often taking extreme behavior interventions can increase psychological pressure. Severe cases may be avoiding social occasions, and avoiding showing their body can lead to social barriers, thereby resulting in a loss of social adaptability[25]. Moreover, a moderate amount of self-adjusting and improving the appearance of behavior can help to improve self-confidence and have a positive impact on the patient's social adaptation[26].

For patients with autologous fat breast augmentation, a lack of confidence in their body and body shape and high self-image concern lead to high self-image pressure. Medical staff can help patients learn to face the pressure of their image in a reasonable way of thinking, pay attention to their values, and establish a new identity model through psychological counseling.

CONCLUSION

The self-image pressure of patients undergoing autologous fat breast augmentation is closely related to their social adaptability. The higher the self-image pressure of the patients, the lower their level of social adaptability. The self-image stress level of the patients was reduced, and their social adaptability problems were reduced. Medical staff need to pay more attention to the psychological state of the patients. Future research should expand the sample size and discuss different types of plastic surgery for the long-term effect on the patient's psychological and social adaptability, which will help to provide patients with individualized and effective plastic surgery services.

FOOTNOTES

Author contributions: Li J conceived and designed this research; Li J and Wang HM wrote the manuscript; Jiang Y, Liu ZN, and He BH collected and organized the materials.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Xinxiang Medical University, No. EC-020-007.

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

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

Data sharing statement: The survey data used in this study can be obtained from the corresponding author upon request.

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

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Che XX

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Observational Study

Correlation between pre-anesthesia anxiety and emergence agitation in non-small cell lung cancer surgery patients

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade C

P-Reviewer: Wu F, United States

Received: March 25, 2024

Revised: May 8, 2024

Accepted: May 16, 2024

Published online: June 19, 2024

Processing time: 85 Days and 23.8 Hours



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Abstract

BACKGROUND

Preoperative anxiety is a common emotional problem during the perioperative period and may adversely affect postoperative recovery. Emergence agitation (EA) is a common complication of general anesthesia that may increase patient discomfort and hospital stay and may be associated with the development of postoperative complications. Pre-anesthetic anxiety may be associated with the development of EA, but studies in this area are lacking.

AIM

To determine the relationship between pre-anesthetic anxiety and EA after radical surgery in patients with non-small cell lung cancer (NSCLC).

METHODS

Eighty patients with NSCLC undergoing surgical treatment between June 2020 and June 2023 were conveniently sampled. We used the Hospital Anxiety and Depression Scale's (HADS) anxiety subscale (HADS-A) to determine patients' anxiety at four time points (T1-T4): Patients' preoperative visit, waiting period in the surgical waiting room, after entering the operating room, and before anesthesia induction, respectively. The Riker Sedation-Agitation Scale (RSAS) examined EA after surgery. Scatter plots of HADS-A and RSAS scores assessed the correlation between patients' pre-anesthesia anxiety status and EA. We performed a partial correlation analysis of HADS-A scores with RSAS scores.

RESULTS

NSCLC patients' HADS-A scores gradually increased at the four time points: 7.33 ± 2.03 at T1, 7.99 ± 2.22 at T2, 8.05 ± 2.81 at T3, and 8.36 ± 4.17 at T4. The patients' postoperative RSAS score was 4.49 ± 1.18 , and 27 patients scored ≥ 5 , indicating that 33.75% patients had EA. HADS-A scores at T3 and T4 were significantly higher in patients with EA (9.67 ± 3.02 vs 7.23 ± 2.31 , 12.56 ± 4.10 vs 6.23 ± 2.05 , $P < 0.001$). Scatter plots showed the highest correlation between HADS-A and RSAS

scores at T3 and T4. Partial correlation analysis showed a strong positive correlation between HADS-A and RSAS scores at T3 and T4 ($r = 0.296, 0.314, P < 0.01$).

CONCLUSION

Agitation during anesthesia recovery in patients undergoing radical resection for NSCLC correlated with anxiety at the time of entering the operating room and before anesthesia induction.

Key Words: Non-small cell lung cancer; Operative treatment; Anesthesiology department; Pre-anesthetic anxiety; Emergence agitation; Correlation study

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Core Tip: This study explored the relationship between anxiety and awakening agitation at four time points (patients' preoperative visit, waiting period in the surgical waiting room, after entering the operating room, and before anesthesia induction), and clarified that emergence agitation in patients undergoing radical surgery for non-small cell lung cancer was related to anxiety at the time of entering the operating room and before anesthesia induction. This finding provides new insights into the management of preoperative anxiety and prevention of postoperative agitation, which can help improve postoperative recovery.

Citation: Yan F, Yuan LH, He X, Yu KF. Correlation between pre-anesthesia anxiety and emergence agitation in non-small cell lung cancer surgery patients. *World J Psychiatry* 2024; 14(6): 930-937

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/930.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.930>

INTRODUCTION

The pathogenesis of lung cancer involves various factors, including smoking, environmental pollution, occupational exposure, exposure to radioactive substances, chronic lung diseases, genetic factors, and decreased immune system function[1,2]. Clinically, treatment strategies for non-small cell lung cancer (NSCLC) are diverse, with surgical resection being the most common and recommended treatment[3]. General anesthesia is commonly used for radical NSCLC surgery and can assist in the smooth implementation of surgery. However, there have been reports indicating the occurrence of emergence agitation (EA) after general anesthesia[4]. EA is an adverse reaction to general anesthesia, characterized by a state of consciousness and behavioral dissociation during the recovery period, manifested as excitement, agitation, disorientation, and inappropriate behavior. It can pose many risks to patients, including falls, bleeding, accidental extubation, and increased hospital costs, adding to the workload of healthcare providers[5].

Excessive stress response, characterized by anxiety, depression, and elevated blood pressure, is the main cause of postoperative EA in patients under general anesthesia. Patients with NSCLC face a higher risk of recurrence and metastasis after undergoing surgical resection[6], often requiring postoperative treatments, such as radiation and chemotherapy. This may lead to psychological stress owing to concerns about the success rate of the surgery and the financial burden, resulting in anxiety, depression, and other negative psychological states. Anxiety is the result of the comprehensive interaction of physiological, psychological, and social factors, which may cause patients to experience intense, excessive, and persistent worries and fears accompanied by physiological panic reactions such as increased heart and respiratory rates[7]. Excessive pre-operative anxiety and tension can increase the risk of developing EA[8].

Several studies have been conducted on children with preoperative anxiety assessment using the modified Yale Anxiety Scale[9,10]. One study has shown a certain positive correlation between preoperative anxiety and postoperative EA[9]. However, owing to the lack of standardized assessment criteria for preoperative anxiety in adults, research in this area is lacking. Furthermore, reports on the relationship between preoperative anxiety and EA mainly involve orthopedic surgery, nasal surgery, and coronary intervention surgery, with few studies focusing on cancer, particularly radical surgery[11,12]. Therefore, this study focused on analyzing the correlation between pre-anesthetic anxiety and EA in patients with NSCLC undergoing surgery under general anesthesia.

MATERIALS AND METHODS

Patient characteristics

Using convenience sampling, 80 patients with NSCLC who underwent surgical treatment between June 2020 and June 2023 were selected.

The inclusion criteria included the following: (1) Definitive diagnosis of NSCLC undergoing surgical treatment; (2) Age ≥ 18 years, any gender; and (3) American Society of Anesthesiologists' physical status classification[13] of grade I or II.

The exclusion criteria included the following: (1) Patients with psychiatric disorders, history of substance abuse, or drug addiction; (2) Patients requiring rescue interventions such as cardiac arrest or multiple organ dysfunction syndrome during surgery; (3) Patients with severe impairment in liver, kidney, heart, or lung function; (4) Patients with visual or auditory impairments before surgery; (5) Patients with tumor metastasis or concurrent malignant tumors; (6) Patients receiving preoperative adjuvant therapies such as radiation or chemotherapy; and (7) Pregnant or lactating women.

Specific method

Anxiety: The Hospital Anxiety and Depression Scale (HADS) is used to screen patients for anxiety and depression in general hospital patients[14]. We used the HADS' anxiety subscale (HADS-A) comprising 7 items to measure patients' anxiety, with each item rated on a four-point scale from 0 to 3. Specifically, a score of 0 indicates no presence of symptoms and 1 indicates mild presence of symptoms, with little or no impact on the individual being assessed, or a mild impact. A score of 2 indicates a moderate presence of symptoms, with some impact on the individual being assessed, and 3 indicates a severe presence of symptoms, with significant frequency and intensity and a severe impact on the individual being assessed. If the total score is 8 or higher, the patient is considered to have anxiety[11].

We assessed patients' anxiety levels at four time points, as follows. T1 (preoperative visit): One day before surgery, a preoperative visit was conducted, informed consent was obtained, communication with the patient was conducted, and the HADS-A was administered. T2 (waiting period in the surgical waiting room): Inside the operating room waiting area, the HADS-A was administered after the patients experienced preoperative fasting, in an unfamiliar operating room environment, and with unfamiliar operating room staff. T3 (after entering the operating room): All patients completed the HADS-A when escorted into the operating room by the operating room nurse and anesthesiologist. T4 (before anesthesia induction): The HADS-A was administered when the mask was placed on the patient's face before anesthesia induction.

Emergence agitation: The Riker Sedation Agitation Scale (RSAS) is used to assess sedation and agitation in post-anesthesia recovery patients. Therefore, we used the RSAS to evaluate patients' EA status. This scale primarily grades the level of agitation based on the behavioral manifestations of patients during the recovery period, using a seven-point scoring system, with a score of 5 or higher indicating the occurrence of EA[15]. Further details are presented in Table 1.

Methods of anesthesia and operation management

Before surgery, the doctor established an intravenous access for the patient, monitored vital signs, and induced intravenous anesthesia using Sufentanil Citrate Injection (0.1-5.0 $\mu\text{g/kg}$, iv), Atracurium Besylate Injection (0.2 mg/kg, iv), and Propofol Medium/Long Chain Fat Emulsion Injection (2 mg/kg, iv). After the patient received oxygen through a face mask, a double-lumen endotracheal tube was placed under direct vision with a disposable adult video laryngoscope using a fiberoptic bronchoscope for precise positioning. Once successfully positioned, the anesthesia machine was connected, and anesthesia was maintained by continuous inhalation of sevoflurane (National Drug Approval H20080681) at a flow rate of 2 L/min. Throughout the surgery, the doctor continuously infused the Sufentanil Citrate Injection (0.15-0.7 $\mu\text{g/kg}$) based on the patient's condition, with intermittent additional doses of Atracurium Besylate as needed to maintain muscle relaxation. The patient's tidal volume was adjusted to 6-8 mL/kg, inspiration-to-expiration ratio was set at 1:2, peak airway pressure was kept below 30 cmH₂O, respiratory rate was maintained at 12-20 breaths per minute, central venous pressure was maintained at 5-12 cmH₂O, mean arterial pressure was maintained above 65 mmHg, and urine output was ensured to be greater than 0.5 mL/kg/h. Vasopressors were used to maintain blood pressure within 20% of the baseline level. All patients underwent temperature monitoring and management. After surgery, patients were provided with intravenous patient-controlled analgesia with weak opioids and non-steroidal anti-inflammatory drugs, along with multimodal analgesia involving the combined use of various drugs to reduce the dosage of individual medications.

Observation index

Observation index: (1) HADS-A scores from T1 to T4; (2) RSAS score and incidence of EA; (3) Differences in HADS-A scores between EA and non-EA patients; and (4) After controlling for age and Numerical Rating Scale (NRS) score, partial correlation analysis between anxiety state and EA. NRS is a numerical representation of pain intensity in which the patient is asked to express the intensity of pain with a number (0-10).

Statistical analysis

We first entered the collected data into Excel for double-checking and analysis; then, we imported it into SPSS 23.0, a statistical software for data analysis. Descriptive statistics using mean \pm SD were employed for continuous data, and *t*-tests were conducted. For categorical data, proportions and frequencies were used and chi-square tests were performed. We created scatter plots of HADS-A and RSAS scores at four time points (T1-T4) to understand whether there was a correlation between pre-anesthesia anxiety levels and EA at these time points. After controlling for the relevant factors, we conducted a partial correlation analysis.

Table 1 Riker Sedation Agitation Scale

Point	Classify	Describe
1	Can't be awakened	The patient has a mild or no response to stimuli and is unable to communicate or follow instructions
2	Very calm	The patient responds to somatic stimuli but is unable to communicate and follow instructions
3	Calm	The patient is drowsy, can be awakened by verbal stimulation or gentle shaking, and can obey simple commands
4	Quiet cooperation	The patient is quiet, easily aroused, and obeys instructions
5	Agitation	The patient is anxious or physically agitated, tries to roll over and get up, can be quieted by verbal cues to discourage him or her
6	Very agitated	The patient requires protective restraint and repeated verbal prompts to discourage
7	Dangerous agitation	The patient pulls on the endotracheal tube, attempts to remove the internal catheter, rolls over the bed rails, unconsciously assaults healthcare workers, and struggles to roll over in the bed, requiring forcible restriction of his movements

RESULTS

Research process

The flow chart of our study is shown in [Figure 1](#).

HADS-A scores of NSCLC patients at the four time points

The HADS-A scores of NSCLC patients gradually increased in all four time points T1~T4, starting from an average of 7.33 ± 2.03 at T1, 7.99 ± 2.22 at T2, 8.05 ± 2.81 at T3, and 8.36 ± 4.17 at T4.

RSAS scores of patients with NSCLC after surgery

The RSAS score of 80 patients with NSCLC after surgical treatment was 4.49 ± 1.18 . A total of 27 patients scored ≥ 5 points, indicating that EA occurred in 33.75% of patients, as shown in [Table 2](#).

Differences in HADS-A scores between EA and non-EA patients

The HADS-A scores at T3 and T4 were significantly higher in patients with EA ($P < 0.05$), as shown in [Table 3](#).

Scatterplot of the HADS-A score and RSAS score

A scatter plot of HADS-A scores *vs* RSAS scores at four time points ([Figure 2](#)) showed that the highest correlation between HADS-A and RSAS scores was found at T3 and T4.

Partial correlation analysis of anxiety state and EA

After controlling for age and NRS scores, a strong positive correlation was observed between anxiety and EA at T3 and T4, as shown in [Table 4](#).

DISCUSSION

Anxiety may increase sensitivity to external stimuli by affecting nervous system regulation, making patients more prone to EA. EA also poses risks such as falls and bleeding[5]. Additionally, patients with EA often require physical restraints or medication interventions, which increase the complexity of care and healthcare personnel workload, adding to the healthcare burden[5,16]. Although EA is generally considered short-lived and self-limiting, its long-term effects on patients during their hospital stay and their traditional implications remain unclear.

The relationship between preoperative anxiety and EA has been the focus of interest in both pediatric and adult patients, although relatively more research has been conducted in children[9,17]. Owing to their psychological and physiological development, children exhibit more pronounced fear and anxiety about surgery and anesthesia, which can lead to a higher incidence of EA postoperatively[17]. In a cross-sectional study of 100 pediatric patients undergoing ophthalmic and otolaryngologic surgeries, the overall incidence of EA in children was 30%, with 34.5% in otolaryngologic surgery and 24.4% in ophthalmic surgery. Higher levels of preoperative anxiety were associated with an increased risk of EA (OR = 1.19, 95%CI 1.06-1.33)[18]. Additionally, Gooden *et al*[19] showed that children with higher preoperative anxiety levels were six times more likely to experience EA than those with lower anxiety levels. Research on the relationship between preoperative anxiety and EA in adult patients is relatively scarce, possibly because adults are generally considered more capable of understanding and coping with surgery and anesthesia processes. However, adult patients may experience preoperative anxiety, which may affect postoperative recovery[20,21]. The assessment and management of preoperative anxiety in adults are equally important; however, more research is needed to explore the relationship between preoperative anxiety and EA in adults, especially in the context of cancer surgery, and effectively managing this issue.

Table 2 Riker Sedation Agitation Scale scores of patients with non-small cell lung cancer after surgery

Point	<i>n</i>	%
1	0	0
2	2	2.5
3	8	10
4	43	53.75
5	10	12.5
6	10	12.5
7	7	8.75
Sum	80	100.00

Table 3 Differences in anxiety subscale of the Hospital Anxiety and Depression Scale scores between emergence agitation and non-emergence agitation patients

Time	EA (<i>n</i> = 27)	non-EA (<i>n</i> = 53)	<i>t</i>	<i>P</i> value
T1	7.59 ± 2.10	7.19 ± 2.41	-0.739	0.462
T2	7.63 ± 1.71	8.17 ± 2.43	1.030	0.306
T3	9.67 ± 3.02	7.23 ± 2.31	-4.015	< 0.001
T4	12.56 ± 4.10	6.23 ± 2.05	-7.556	< 0.001

EA: Emergence agitation.

Table 4 Partial correlation analysis of anxiety and emergence agitation

Time	Partial correlation analysis	
	<i>r</i>	<i>P</i> value
T1	0.098	0.396
T2	0.042	0.713
T3	0.296	0.008
T4	0.314	0.005

We investigated the anxiety levels of patients with NSCLC during preoperative visits, in the waiting room, after entering the operating room, and before anesthesia induction. We found that patients' anxiety levels showed an increasing trend, reflecting their growing concerns and fears about surgery as the operation progressed. This is consistent with the study by Kuzminskaitė *et al*[22], wherein most patients perceive the day of surgery as the most critical and potentially risky moment in their lives, leading to anxiety levels ranging from 11% to 93% and experiencing varying degrees of anxiety before surgery. This anxiety stems from fear of the unknown, concerns about surgical outcomes, and worries about their safety.

Older individuals are also more likely to develop EA. Owing to organ function degeneration, older patients have a lower tolerance to surgery and anesthesia. Postoperative pain is a risk factor for EA[23]. Therefore, after excluding interfering factors such as age and postoperative pain, we found no significant correlation between anxiety levels during preoperative visits or in the preoperative waiting room and the occurrence of EA. However, there was a correlation between anxiety levels after entering the operating room and before anesthesia induction, and EA. This further confirms that preoperative anxiety directly influences the occurrence of EA. The operating room and anesthesia induction process may have a more direct and pronounced impact on patients' emotions. The unfamiliar environment of the operating room, tense atmosphere before surgery, and effects of anesthetic drugs can trigger more pronounced anxiety in patients, affecting their recovery. Anesthetic agents such as sevoflurane have sedative and hypnotic effects, which may lead to adverse reactions such as agitation during recovery, potentially increasing the risk of emergence agitation when patients experience anxiety while receiving these medications[24].

Therefore, we recommend conducting thorough preoperative visits and patient preparation. During the visit, it is important to actively communicate with the patient and provide detailed information about the anesthesia methods, surgical procedures, and relevant cases to alleviate preoperative anxiety, improve the patient's emotional state, enhance

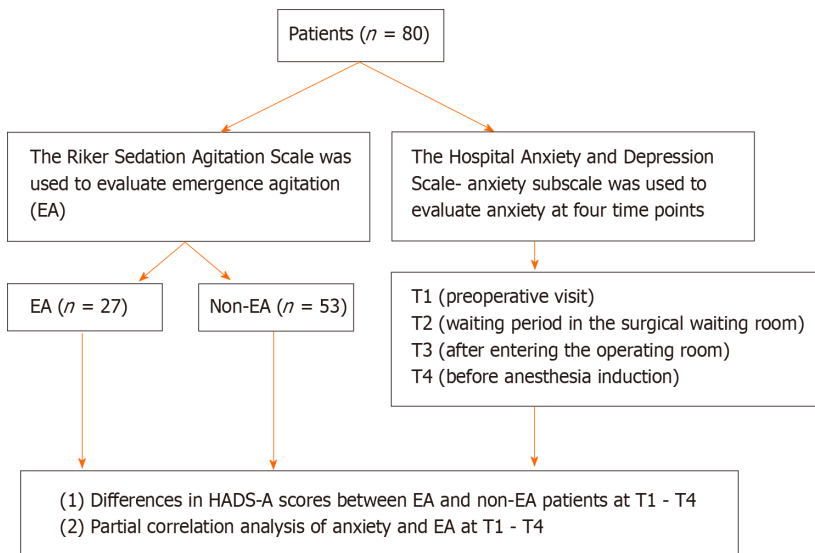


Figure 1 Research flow chart. EA: Emergence agitation; HADS-A: Anxiety subscale of the Hospital Anxiety and Depression Scale.

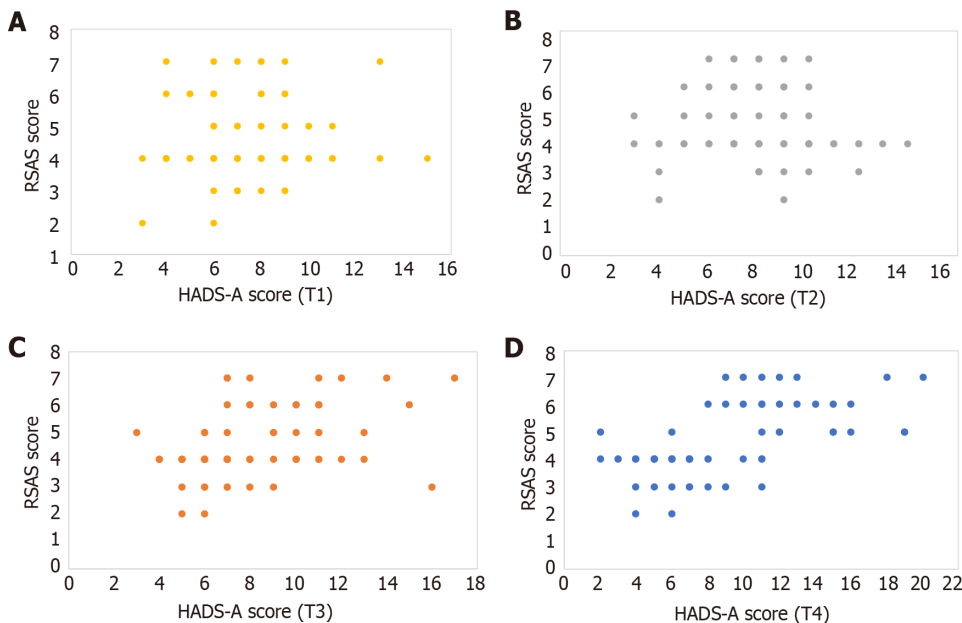


Figure 2 Scatterplot of anxiety subscale of the Hospital Anxiety and Depression Scale scores and Riker Sedation Agitation Scale scores.

A: T1; B: T2; C: T3; D: T4. RSAS: Riker Sedation Agitation Scale; HADS-A: Anxiety subscale of the Hospital Anxiety and Depression Scale.

their positivity for surgery, and prevent emergence agitation due to negative emotions. Before entering the operating room and inducing anesthesia, healthcare professionals can take measures such as deep breathing, relaxation training, and distraction techniques to help patients manage their anxiety. These skills can help patients relax their minds and bodies and reduce their feelings of anxiety.

CONCLUSION

Anxiety can potentially affect the effectiveness of anesthesia and smooth progression of surgery, and is also associated with EA. By assessing the anxiety levels of patients with NSCLC at multiple time points, we can gain a more comprehensive understanding of the dynamic changes in their anxiety states, confirming that patient EA is related to anxiety levels upon entering the operating room and before anesthesia induction. Compared with existing research, this study may reveal new opportunities for anxiety assessment and intervention timing, offering a fresh perspective for future studies.

FOOTNOTES

Author contributions: Yan F and Yu KF conceived the project and wrote the manuscript; Yuan LH and He X acquired and analyzed the data; all authors contributed to the article and approved the submitted version.

Institutional review board statement: This study was reviewed and approved by the Wuhan Pulmonary Hospital Institutional Review Board.

Informed consent statement: All participants have signed informed consent forms.

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

Data sharing statement: The anonymous data used in this study can be obtained from the corresponding author upon request.

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

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S-Editor: Gong ZM

L-Editor: A

P-Editor: Che XX

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Prospective Study

Clinical efficacy of Baijin pills in the treatment of generalized tonic-clonic seizure epilepsy with cognitive impairment

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Rondon MB, United States

Received: March 1, 2024

Revised: April 22, 2024

Accepted: April 25, 2024

Published online: June 19, 2024

Processing time: 110 Days and 5.3 Hours



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Abstract

BACKGROUND

The generalized tonic-clonic seizure (GTCS) is the most usual variety of epileptic seizure. It is mainly characterized by strong body muscle rigidity, loss of consciousness, a disorder of plant neurofunction, and significant damage to cognitive function. The effect of antiepileptic drugs on cognition should also be considered. At present, there is no effective treatment for patients with epilepsy, but traditional Chinese medicine has shown a significant effect on chronic disease with fewer harmful side effects and should, therefore, be considered for the therapy means of epilepsy with cognitive dysfunction.

AIM

To investigate the clinical efficacy of Baijin pills for treating GTCS patients with cognitive impairment.

METHODS

This prospective study enrolled patients diagnosed with GTCS between January 2020 and December 2023 and separate them into two groups (experimental and control) using random number table method. The control group was treated with sodium valproate, and the experimental group was Baijin pills and sodium valproate for three months. The frequency and duration of each seizure, the Montreal Cognitive Assessment Scale (MoCA), and the Quality of Life Rating Scale (QOLIE-31) were recorded before and after treatment.

RESULTS

There were 85 patients included (42 in the control group and 43 in the experi-

mental group). After treatment, the seizure frequency in the experimental group was significantly reduced ($P < 0.05$), and seizure duration was shortened ($P < 0.01$). The total MoCA score in the experimental group significantly increased compared to before treatment ($P < 0.01$), and the sub-item scores, except naming and abstract generalization ability, significantly increased ($P < 0.05$), whereas the total MoCA score in the control group significantly decreased after treatment ($P < 0.05$). The QOLIE-31 score of the experimental group increased significantly after treatment compared to before treatment ($P < 0.01$).

CONCLUSION

Baijin pills have a good clinical effect on epilepsy with cognitive dysfunction.

Key Words: Epilepsy; Generalized tonic-clonic seizure; Cognitive impairment; Traditional Chinese medicine; Baijin pills

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Core Tip: Generalized tonic-clonic seizure can induce the most significant damage to cognitive function. The impact of antiepileptic drugs on cognition should not be ignored. At present, there is no special treatment for patients with epilepsy, and traditional Chinese medicine has shown a significant effect on chronic diseases with fewer harmful side effects; therefore, traditional Chinese medicine should be considered for the treatment of epilepsy with cognitive dysfunction. Baijin pills have a positive clinical effect on patients with epilepsy and cognitive dysfunction.

Citation: Li JB, Jiang J, Xue L, Zhao S, Liu HQ. Clinical efficacy of Baijin pills in the treatment of generalized tonic-clonic seizure epilepsy with cognitive impairment. *World J Psychiatry* 2024; 14(6): 938-944

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/938.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.938>

INTRODUCTION

Epilepsy is a common type of neurological disorder disease. It is a chronic disease that is associated with temporary brain dysfunction. Sudden abnormal discharge of brain neurons caused by various triggers is its primary pathogenesis[1]. Although different brain discharge sites cause different clinical symptoms, the core features are transient, paroxysmal, stereotypical, and repetitive[2]. Cognitive dysfunction is a common clinical symptom associated with epilepsy patients, whether in newly diagnosed patients or patients with long-term epilepsy; cognitive dysfunction is common[3]. Cognitive impairment occurs in greater than 1/3 of patients with epilepsy and in up to 70%-80% of patients with chronic epilepsy [4]. Defects in the cognitive function of epilepsy patients, such as a slow pace of thinking and loss of memory, attention, and language, can cause different levels of interference in social interaction, which can make it impossible for patients to enjoy socializing fully, thus reducing their quality of life[5]. Epileptic seizures have caused great pain to the patient's body and mind, significantly reducing their quality of life. The decline in knowledge retention further reduces the quality of the patient's life, and self-harm and harm to others can occur in some epileptic patients, causing serious social problems. If the focus is only on the treatment of epileptic seizures but not on the cognitive, psychological, as well as social aspects of epilepsy, the patient, their family, and their broader community could suffer the negative consequences.

The generalized tonic-clonic seizure (GTCS) is the most common variety of seizure in epilepsy and is mainly characterized by strong body muscle rigidity, loss of consciousness, a disorder of plant neurofunction, and the most significant damage to cognitive function[6,7]. Sodium valproate is a traditional, low-cost, broad-spectrum antiepileptic drug with low application. It is the first-line drug in GTCS and multiple other types of epilepsy. With the development of biopsychosocial medicine, the ideal treatment outcome of epilepsy treatment is to up to simple control and reduction of events and to maximize the patient's quality of life. Therefore, treating cognitive dysfunction is very important to epilepsy patients. There are few available and effective methods for treating epilepsy, but AEDs themselves have been shown to impair cognition, especially the traditional antiepileptic drugs (AEDs)[8]. The factors affecting the cognitive function of epilepsy patients are generally summarized as following: etiology, epileptic seizures, interictal epileptiform discharges, neuronal network, AEDs, and surgery while controlling epilepsy and AEDs are more manageable factors[6,9,10]. The impact of AEDs on cognition should not be ignored. At present, there is no special treatment for patients with epilepsy, and traditional Chinese medicine has shown a significant effect on chronic diseases with fewer harmful side effects; therefore, traditional Chinese medicine should be considered for the treatment of epilepsy with cognitive dysfunction. From a Chinese traditional medical point of view, "Sputum" is a common pathological factor in the development of epilepsy and cognitive dysfunction; both can be treated by sputum. Baijin pills are made up of alumen (Bai Fan in Chinese) and *Curcumae Radix* (Yu Jin in Chinese), which are made up of drugs with the ability to affect the mind, heart, spittoon, epilepsy, sudden syncope, and mass salivation. It is also useful for treating laryngeal and acute tonsillitis. Modern Chinese medicine clinical Baijin pills are used in many diseases such as epilepsy, schizophrenia, hyperlipidemia, arrhythmias, and hepatobiliary disease. This study chose the most severe GTCS and the most widely used AED, sodium valproate, as the basis for research on the clinical effect of using Baijin pills for GTCS with cognitive

impairment and observation of its clinical efficacy.

MATERIALS AND METHODS

This prospective study was confirmed by the Department of the Nanjing University of Chinese Medicine. The ethics committee of our hospital agreed to conducting this study. The informed consent form was obtained from the participated before enrolling the study.

Patient recruitment and selection criteria

We enrolled patients diagnosed with GTCS between January 2020 and December 2023. The inclusion criteria were as follows: (1) Meeting the diagnostic criteria of epilepsy in Western and Chinese medicine[11]; (2) Age ≥ 18 years and ≤ 70 years; (3) Duration of epilepsy ≥ 2 years, with ≥ 1 major seizure per month; (4) Montreal Cognitive Assessment Scale (MoCA) Scale score < 26 points; and (5) Signed informed consent, and good compliance. Patients who met the following criteria were excluded from the study: (1) Pregnant and lactating women and women of childbearing age; (2) Serious primary diseases of the heart, lungs, liver, kidneys, and/or bone marrow; (3) Mental disorders; (4) Failure to follow the study requirements or write disease records; and (5) Clinical observation of other drugs in the past year.

Study design

This is a prospective study. Eligible patients were enrolled and separated into two groups (experimental and control) using the random number table method. The control group was therapied with sodium valproate, and the experimental group was therapied with Baijin pills and sodium valproate treatment for six months. The frequency and duration of each seizure before and after treatment were recorded. The Montreal Cognitive Assessment Scale (MoCA) and Quality of Life Rating Scale (QOLIE-31) were used before and after treatment[12]. QOLIE-31 is the scale consisting of 31 questions, divided into 7 aspects and 1 comprehensive entry. It provides a rapid and comprehensive assessment of the major health-related quality of life issues of concern to adults with epilepsy and can be used in clinical trials to evaluate patient response to changes in treatment regimens. The higher the score, the better the quality of life. Sodium valproate (Hunan Xiangzhong Pharmaceutical Co., Ltd.; lot No. H43020874, 200 mg/tablet) was used as follows: An initial dose of 600 mg/d, three times/d, gradually increased to 1200 mg/d, three times/d[11]. Patients in both groups were not allowed to take any other drugs that had an impact on epilepsy or cognition during treatment. The control group was therapied with conventional sodium valproate for six months. The other group was therapied with conventional sodium valproate plus the Baijin pill treatment. Patients in the two groups were followed up once a month from the beginning of treatment, and seizures were recorded, including the number and duration of seizures. A general physical examination and a detailed nervous system examination were performed; three routine biochemical and electrocardiogram examinations were performed, and the therapeutic effect was evaluated three months later.

Epileptic seizures

The frequency and duration of each seizure were recorded before and after three months of treatment in both groups. The difference between seizure frequency and duration was based on the pre-treatment and post-treatment levels. Changes in epileptic seizures before and after treatment were observed and compared between the two groups.

Cognitive function

The two groups of epilepsy patients were evaluated using the MoCA scale before and after treatment, changes in cognitive function before and after treatment were observed, and the changes between the two groups were compared. One point was added if the number of years of schooling was less than 12. All the scales were assessed by the same physician.

Quality of life

The Chinese version of the Adult Epilepsy Quality of Life Scale (QOLIE-31) was used to measure the efficacy evaluation criteria before and after treatment, to observe the changes in patients' quality of life before and after treatment, and to compare the changes between the two groups. QOLIE-31 score difference = pre-treatment level-post-treatment level. All the scales were assessed by the same physician.

Statistical analysis

All data were processed using SPSS20.0 statistical software. The χ^2 test was used for counting data, and expression was used for measurement data. Paired *t*-tests were used before and after treatment in the same group, and two independent sample *t*-tests were used for comparisons between groups. The significance level was set at $P < 0.05$.

RESULTS

Patient characteristics

Eighty-five patients were included: 42 in the control group and 43 in the experimental group. Five patients dropped out

of the group or were lost to follow-up: Two patients in the experimental group dropped out due to rash and poor medical compliance; one patient in the control group showed valproate encephalopathy regression, and one case each in the experimental and control groups dropped out for unknown reasons (Table 1).

Comparison of seizure frequency, seizure duration, and difference before and after treatment

After treatment, the frequency of seizures in the experimental group was significantly reduced ($P < 0.05$), and the duration of seizures was shortened ($P < 0.01$). The decrease in seizure frequency in the experimental group was significantly greater than in the control group ($P < 0.05$), and the reduction in seizure duration in the experimental group was significantly greater than in the control group ($P < 0.01$; Table 2).

Comparison of MoCA scale scores before and after treatment

After treatment, the total MoCA score in the experimental group was significantly higher than before treatment ($P < 0.01$). The sub-item scores, except naming and abstract generalization ability, were significantly increased ($P < 0.05$). In contrast, the total MoCA score in the control group was significantly decreased compared with before treatment ($P < 0.05$; Table 3).

Comparison of QOLIE-31 scores before and after treatment between the two groups and the difference of scores before and after treatment

The quality of life score in the experimental group increased significantly after treatment compared to that before treatment ($P < 0.01$). The QOLIE-31 score in the control group also increased significantly compared to that before treatment ($P < 0.05$), and the QOLIE-31 score of the experimental group increased more than that of the control group ($P < 0.01$); the difference was statistically significant (Table 4).

DISCUSSION

Epilepsy is a clinical syndrome characterized by unpredictable and transient central nervous system dysfunction caused by synchronized abnormal discharge of brain neurons with different triggers. Epilepsy is a common chronic disease affecting about 50 million people. The prevalence rates of epilepsy are 5.8‰ in developed countries and 15.4‰ in developing countries[13].

The pathogenesis of epilepsy is complex and primarily involves neurotransmitters, ion channels, immune or inflammatory responses, and abnormal neural pathways. The neurotransmitter mechanism is mainly an imbalance between Glu-mediated excitation and GABA-mediated inhibition. Other neurotransmitters such as serotonin, norepinephrine, and dopamine also play a role in the pathogenesis of epilepsy[14]. An imbalance in ion charge caused by abnormal ion channels can induce epilepsy. Inflammatory cytokines are involved in the pathogenesis of epilepsy, and glial cells play a role in regulating immune and inflammatory responses during epilepsy. It has been found that inflammatory cytokines have harmful effects on neurons, altering their excitability, producing toxic mediators, and increasing the impermeability of the blood-brain barrier. Abnormal hippocampal neurogenesis and brain injury lead to the generation of new neural circuits, which is also important in the pathogenesis of epilepsy[15,16]. Epilepsy is a complex disease, and the challenges people face are not just the damage and suffering caused by the seizures. Epilepsy may also be accompanied by a series of comorbidities that have bad impact on the patient's health and quality of life. Common epileptic comorbidities include cognitive dysfunction, such as memory, attention, or processing problems; mental health conditions, including depression or anxiety; and somatic comorbidities, such as sleep disorders and migraines[17-19]. Comorbidities are common and for many patients with epilepsy, they are often more serious than the harm caused by seizures. Cognitive dysfunction is one of the most common and distressing epileptic comorbidities. The literature reports that different degrees of cognitive dysfunction exist in more than one-third of epilepsy patients, and the incidence of cognitive impairment in patients with a long history of epilepsy can reach 70%-80%[20,21].

Out of all the seizure types, the GTCS is the most serious type of seizure associated with cognitive impairment. The GTCS, also known as a grand mal seizure, is the most prominent form of seizure. One of the main reasons is that during the onset of GTCS, the muscles of the whole body are tetanic and convulsive, with extreme energy consumption, and apnea during the onset causes the brain tissue to be in a state of severe hypoxia[22,23]. Of all the organs, the brain is the most sensitive to hypoxia. The hippocampus, which is closely related to cognition, is the most sensitive region[24-26].

Sodium valproate is routinely used for clinical treatment. The study results showed that the number and duration of seizures in the control group after sodium valproate treatment alone were reduced compared to those before treatment. The effect of sodium valproate on seizure control was satisfactory, but epilepsy was not completely cured and the patient still had some less severe seizures, and the cognitive damage of epilepsy was still aggravated. Therefore, the total MoCA score in the control group after treatment was lower than that before treatment, which did not indicate that sodium valproate had a damaging effect on cognition. Therefore, the relationship between sodium valproate levels and cognition requires further research. Platinum pills with alum and stasis gold as the main ingredients can clear phlegm, clear the heart, and calm the mind, and are used for spittoon choking, epilepsy, sudden fainting, and hypersalivation. It also treats laryngeal wounds, milk moths, and other diseases. Modern Chinese medicine clinical platinum pills have been used for the treatment of epilepsy, schizophrenia, hyperlipidemia, arrhythmias, hepatobiliary disease, and many other diseases. This study showed that platinum pills have good clinical efficacy in treating the syndrome of phlegm-turbidizing obstruction of the GTCS accompanied by cognitive dysfunction. From the perspective of seizure control, the seizure frequency in the experimental group was significantly reduced after treatment ($P < 0.05$), the seizure duration was

Table 1 Characteristics of patients

	Experimental group	Control group
Sample size	40	40
Female	20	18
Age (yr)	40.92 ± 13.51	42.37 ± 12.3
Clinical course	5.65 ± 2.34	5.91 ± 1.62
Education background		
Bachelor's degree or above	8	10

Table 2 The frequency, duration, and difference of seizures before and after treatment were compared between the two groups

Group	Sample size	Period	Attack frequency/6 months	Seizure duration (min/time)
Experiment group	40	Before treatment	12.60 ± 6.00	3.55 ± 1.75
		After treatment	8.77 ± 5.75	1.62 ± 1.55
		The difference before and after treatment	3.82 ± 1.53	2.49 ± 0.83
Control group	40	Before treatment	12.98 ± 6.26	3.75 ± 1.69
		After treatment	9.45 ± 5.99	2.12 ± 1.81
		The difference before and after treatment	2.72 ± 2.18	1.48 ± 0.75

Table 3 Comparison of Montreal Cognitive Assessment Scale scores before and after treatment between the two groups

Group	Experiment group (n = 40)		Control group (n = 40)	
	Before treatment	After treatment	Before treatment	After treatment
MoCA total score 30	18.25 ± 2.34	20.43 ± 2.65	17.65 ± 2.16	16.53 ± 1.98
Memory ability 5	2.75 ± 0.81	3.15 ± 0.96	2.64 ± 0.79	2.40 ± 0.73
Verbal fluency 3	2.13 ± 0.78	2.52 ± 0.92	2.06 ± 0.77	1.97 ± 0.72
Visuospatial execution ability 5	2.98 ± 0.59	3.27 ± 0.70	2.87 ± 0.61	2.71 ± 0.58
Naming capability 3	2.10 ± 0.81	2.30 ± 0.85	2.07 ± 0.79	1.94 ± 0.77
Attention and calculation ability 6	3.05 ± 0.78	3.42 ± 0.84	3.01 ± 0.76	2.74 ± 0.72
Orientation ability 6	4.02 ± 0.89	4.45 ± 0.93	3.94 ± 0.85	3.79 ± 0.81
Ability of abstraction and generalization 2	1.09 ± 0.45	1.31 ± 0.56	1.04 ± 0.49	0.95 ± 0.42

Table 4 The Quality of Life Rating Scale (QOLIE-31) score before and after treatment and the difference between the two groups

Group	Sample size	Period	QOLIE-31 score
Experiment group	40	Before treatment	43.32 ± 7.45
		After treatment	51.46 ± 8.12
		The difference before and after treatment	9.44 ± 5.23
Control group	40	Before treatment	44.56 ± 6.92
		After treatment	48.42 ± 7.83
		The difference before and after treatment	4.26 ± 4.78

shortened ($P < 0.01$). The platinum pill combined with sodium valproate has a better effect on seizure control than sodium valproate alone; therefore, the platinum pill has an antiepileptic effect. From the point of view of the impact on cognitive function, the MoCA score in the experimental group was significantly increased after treatment ($P < 0.01$). The scores of subitems except naming and abstract generalization ability were significantly increased ($P < 0.05$), while the total MoCA score in the control group was decreased after treatment ($P < 0.05$). The platinum pill has a significant positive effect on cognitive dysfunction associated with epilepsy. In terms of quality of life, the QOLIE-31 scale score in the experimental group significantly increased after treatment ($P < 0.01$), and the QOLIE-31 scale score in the experimental group was significantly higher than that of the control group ($P < 0.01$). The degree of improvement due to platinum pills combined with sodium valproate on the quality of life of patients with epilepsy is significantly higher than that of sodium valproate alone because the addition of sodium valproate combined with Diitan decoction can improve the control of seizures and cognitive function, further improving the quality of life of patients.

Our study had a number of limitations. First of all, the sample size is not large enough, and a larger sample size study is needed to verify the test results. Second, the study was not a multicenter randomized controlled trial. So our findings should be treated with caution.

CONCLUSION

AEDs and epileptic seizures damage cognitive function, and there is currently no specific treatment for epileptic cognitive impairment in Western medicine; therefore, Chinese medicine is a possible new treatment method. Considering that "phlegm" is the common pathological factor of epilepsy and cognitive impairment in traditional Chinese medicine, it is possible to treat epilepsy with cognitive dysfunction based on phlegm. The results showed that Baijin pills have a good clinical effect on epilepsy with cognitive dysfunction.

FOOTNOTES

Author contributions: Li JB and Liu HQ contributed equally to this work; Li JB, Jiang J, Xue L, Zhao S and Liu HQ designed the research study; Li JB, Jiang J, Xue L, Zhao S and Liu HQ performed the research; Jiang J, Xue L, Zhao S contributed new reagents and analytic tools; Li JB and Liu HQ analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

Supported by Jiangsu Province Phase 6 "333 Project", No. BRA202201.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Committee of the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine Ethics Committee.

Clinical trial registration statement: Clinical trials registered in researchregistry (www.researchregistry.com).

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

Conflict-of-interest statement: Dr. Liu has nothing to disclose.

Data sharing statement: There is no additional data available.

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

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S-Editor: Lin C

L-Editor: A

P-Editor: Che XX

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Randomized Clinical Trial

Problem-solving model guided by stimulus-organism-response theory: State of mind and coping styles of depressed mothers after cesarean delivery

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Rana S, India

Received: April 10, 2024

Revised: May 6, 2024

Accepted: May 24, 2024

Published online: June 19, 2024

Processing time: 70 Days and 0.8 Hours



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Abstract

BACKGROUND

The use of a problem-solving model guided by stimulus-organism-response (SOR) theory for women with postpartum depression after cesarean delivery may inform nursing interventions for women with postpartum depression.

AIM

To explore the state of mind and coping style of women with depression after cesarean delivery guided by SOR theory.

METHODS

Eighty postpartum depressed women with cesarean delivery admitted to the hospital between January 2022 and October 2023 were selected and divided into two groups of 40 cases each, according to the random number table method. In the control group, the observation group adopted the problem-solving nursing model under SOR theory. The two groups were consecutively intervened for 12 weeks, and the state of mind, coping styles, and degree of post-partum depression were analyzed at the end of the intervention.

RESULTS

The Edinburgh Postnatal Depression Scale and Hamilton Depression Scale-24-item scores of the observation group were lower than in the control group after care, and the level of improvement in the state of mind was higher than that of the control group ($P < 0.05$). The level of coping with illness in the observation group after care (26.48 ± 3.35) was higher than that in the control group (21.73 ± 3.20), and the level of avoidance (12.04 ± 2.68) and submission (8.14 ± 1.15) was lower than that in the control group (15.75 ± 2.69 and 9.95 ± 1.20), with significant differences ($P < 0.05$).

CONCLUSION

Adopting the problem-solving nursing model using SOR theory for postpartum depressed mothers after cesarean delivery reduced maternal depression, improved their state of mind, and coping level with illness.

Key Words: Stimulus-organism-response theory; Problem solving model; Cesarean section; Postpartum depression

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Core Tip: Reasonable and effective nursing interventions play a pivotal role in alleviating an individual's psychological burden and elevating their overall state of mind. This is particularly crucial for postpartum mothers who are suffering from depression after undergoing a cesarean delivery, as it can significantly contribute to their emotional recovery and well-being.

Citation: Yuan RF, Jiang MQ, Li J, Zhang JJ. Problem-solving model guided by stimulus-organism-response theory: State of mind and coping styles of depressed mothers after cesarean delivery. *World J Psychiatry* 2024; 14(6): 945-953

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/945.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.945>

INTRODUCTION

Postpartum depression is a common affective disorder type of disease in the puerperium of postpartum women. Women in the postpartum 6 week such experience irritability, depression, sadness, frustration, and other psychological states, and even some patients have symptoms such as hallucinations and negativity, which significantly affect the adaptive process of women's role transition, so that their self-efficacy is reduced, causing serious psychological problems and affecting their state of mind[1,2]. Nursing intervention is an important solution that affects the psychological state of an individual, and the use of reasonable and efficient nursing measures can improve the postpartum state of mind and improve the way of postpartum depressed mothers to cope with the disease. The total detection rate of postpartum depression among elderly women in China is 20.0%[3]. The prevalence of postpartum depression among women ranges from 5%–26% and is the main cause of disability and suicide in the first year of the postpartum period among women worldwide[4]. In recent years, the number of psychosocial and physiological studies on postpartum depression has increased with the increasing prevalence of postpartum depression. Improving the psychological function and perinatal outcomes of postpartum depressed mothers has been studied extensively reported. However, the processes and effects of each intervention method vary, and there is a lack of corresponding normative standards. The stimulus-organism-response (SOR) theory is an important branch of modern social psychology that was first proposed in 1988 by the social psychologist Tesser AI, and consists of three parts: Stimulus, organism, and behavioral response. It was widely used in the field of psychology to promote the individual self-esteem, improve the level of individual emotional management, and quality of life[5]. This theory believes that individual behavior is influenced by individual and social guidance, contradictory behaviors between the individual and the social environment, and emphasizes the systematic and dynamic nature of individual psychological problems, wherein the stimulus (S) indicates the external environmental factors of the organism (O), which acts as a mediator variable to represent the individual's change in psychological state, such as affective or cognitive responses, and the response (R) is the outcome of the individual's attitude or behavior variables. Mastery of SOR theory can provide an effective way to cope and deal with psychological problems. The use of conventional care alone lacks systematicity and specificity owing to the many risk factors that lead to postpartum depression, while holistic care is too general, resulting in sub-optimal problem solving. Therefore, this study adopted problem-solving nursing measures based on SOR theory and corresponding nursing interventions to improve the effectiveness of nursing interventions. In this study, we used women with postpartum depression after cesarean section as the case object, and analyzed the application effect of the problem-solving nursing model under the guidance of SOR theory.

MATERIALS AND METHODS

Eighty cases of postpartum depression after cesarean delivery admitted to the hospital from January 2022 to October 2023

Table 1 Comparing basic information of two groups

Factor	Observation (n = 40)	Control (n = 40)	χ^2	P value
Age (year)			0.503	0.478
≤ 35	25	28		
> 35	15	12		
Number of births			0.808	0.369
Primigravida	24	20		
Menstruation	16	20		
Education			0.774	0.679
Junior high and below	10	8		
High school	23	22		
College and above	7	10		
Fetal gender			0.201	0.654
Male	22	20		
Female	18	20		
Profession			0.863	0.650
Fixed profession	12	15		
Freelance	18	18		
Unemployed	10	7		
Weeks of pregnancy	39.92 ± 1.02	40.01 ± 1.05	0.151	0.698
BMI (kg/m ²)	23.04 ± 1.84	22.96 ± 1.94	0.036	0.850

BMI: Body mass index.

were selected, and the inclusion criteria were: (1) All the included mothers underwent cesarean section in the hospital, which was caused by fetal malposition, low amniotic fluid and other factors, and was not owing to pregnancy complications; (2) singleton pregnancy; (3) conforming to the criteria for the determination of post-partum depression[6]; (4) each of them were in the first year of the postpartum period; and (5) all the mothers were informed of the specific details and contents of the study and signed a consent form. The exclusion criteria were as follows: (1) Prenatal ultrasound suggesting concomitant fetal malformations, fetal growth restriction, and other diseases; (2) newborns requiring resuscitation and treatment; (3) gestational hypertension, eclampsia, diabetes, and other diseases; (4) major physical dysfunctions; (5) mental disorders, such as anxiety and depression prior to the cesarean section; (6) malignancy; and (7) major adverse events, such as the death of a loved one.

The mothers were divided into two groups according to the random number table method, and there was no significant difference in the comparison of the basic information of each group ($P > 0.05$; Table 1).

Methods

The control group adopted conventional care; that is, instructed mothers to correctly apply antidepressant drugs; nursing staff communicate effectively with mothers, listening patiently to their psychological state, guiding them to analyze the reasons for the emergence of adverse psychological state, and encouraging them to cope with it positively; explaining to mothers the reasons for postnatal depression, and conducting psychological counselling; leading mothers to adapt to the role and gradually change; encouraging mothers to insist on breastfeeding, and increase touch and play activities between mothers and newborn babies to promote parent-child communication. Increase maternal and newborn babies' touch and play activities to promote parent-child communication.

The observation group adopted the problem-solving nursing model under the guidance of the SOR theory based on the control group. (1) Formation of the SOR care team: The team consists of doctors, nurses and psychologists. The doctor is responsible for diagnosing and treating the mother's condition, the nurse is responsible for health promotion, and the psychologist is responsible for psychological counselling; (2) External stimulation: One-on-one communication is needed before the birth of the baby to understand the misconceptions about postnatal rehabilitation and infant feeding, and then to summarise the issues raised. Postnatal rehabilitation care includes postnatal observation and postnatal complications, as well as postnatal recovery and sleep quality. In addition, they need to communicate with patients in a warm manner, give them psychological comfort, and encourage them to vent their negative emotions; (3) Cognition and emotion: For the postpartum problems in the recovery process, we need to provide targeted care: before discharge, mothers can scan the

code to join the home rehabilitation WeChat group, and real name system; for the problems arising in home rehabilitation group members regularly live broadcasting to implement health education, 40 min/session; and postpartum can be used to implement the study of WeChat public number, and in the public number of regular dissemination of relevant nursing information, during the process, mothers can according to their own needs, and the public information can be distributed. In the process, mothers can ask questions to the nursing staff according to their own needs, and then the nursing staff will give them targeted answers; (4) Peer education can be carried out on a regular basis, usually by inviting mothers who have successfully recovered, and then training them, allowing them to share their own experiences, and then letting other people learn about it; (5) Mothers need to be encouraged to learn how to take care of the newborns, to improve their own nursing skills and to enhance their sense of satisfaction, so that they can learn as soon as possible, and then they can be encouraged to learn how to care for the newborns; (6) Mothers need to be encouraged to learn how to care for newborns, to improve their own caregiving skills, and to increase their sense of self-satisfaction, so that they can enter the role of motherhood as soon as possible; and (7) After discharge from the hospital, the nursing staff should instruct the mothers to follow the rehabilitation support programme, carry out self-monitoring on a daily basis, and then summarize the rehabilitation status of the day and make improvements to the rehabilitation programme for the next day.

Problem assessment

The nursing staff communicated with the mother and her family to create a quiet and private environment, and the content of the problem assessment and survey was kept confidential to protect the mothers' privacy. Nursing staff used unstructured interview methods to conduct the assessment and investigation, on-site audio recording and recording of the survey content, and initially asked "How do you feel recently?". The nursing staff used an unstructured interview method to conduct the assessment and survey and recorded the content of the survey by initially asking "How do you feel recently?", so that they could freely explain their feelings and gradually extend the topic to mother-in-law-daughter-in-law relationships, husbands and wives, family economy, childcare, postnatal rehabilitation, and other issues to clearly identify the relevant issues that may induce and aggravate postnatal depression, and to provide a reference basis for the next step of care.

External stimulation

According to information from the survey and assessment, common problems of home rehabilitation for mothers include cesarean section incision recovery, scientific childcare, postpartum physical recovery, and mother-in-law and husband-wife relationships. We assessed the degree of maternal awareness of postpartum depression by examining the distribution of health brochures, scientific lectures, and one-on-one communication methods. We briefly explained that the caesarean section has no obvious negative impact on later life, establishing a correct view of childbearing, explaining the erroneous thinking of favoring sons over daughters, and emphasizing the equality of men and women and knowledge of genetics. Mothers were guided to participate more in newborn care and early contact between mothers and their babies was emphasized. A relaxed and pleasant family atmosphere was encouraged by reducing the impact of external stimuli on the mother, such as crying babies and quarrels between husband and wife; encouraging the mother to participate in more work and recreational gatherings after her discharge from the hospital; and helping the mother to take on childcare work to divert the mother's attention and alleviate her psychological and physiological burdens.

Cognitive and emotional wellbeing

Strengthening couples' health management by organizing one-on-one communication between mothers and their husbands; encouraging mothers to frankly explain their psychological state, demands, and dissatisfaction with daily life; and reminding husbands to listen to mothers' demands more often. For example, husbands are unable to play a coordinating role in mother-in-law-daughter-in-law relations, adopting an avoidant attitude and avoiding positive communication with their wives and mothers; husbands do not understand their wives and cannot share household chores in husband-and-wife relations; and both husbands and wives lack experience in parenting in terms of child-rearing; for example, they do not know what to do when their children are crying and are only fed up with the situation. Therefore, we have done a good job of health education for the husbands of women who have given birth, and we have provided them with scientific information and analysis of the postnatal emotional changes so that the husbands can accurately understand postnatal depression. At the same time, we have done a good job of training husbands and mothers in the skills of caring for their newborn babies, stressing the importance of breastfeeding, and mastering the basic measures of bathing and feeding newborn babies, so that the husbands can actively take on the basic tasks of crying, feeding milk powder, and changing nappies.

Psychological counselling: Mothers are given explanations of postpartum physical rehabilitation measures (such as postpartum yoga and postpartum gymnastics) and measures for the care of incisions after caesarean section to reduce the psychological burden on mothers through the distribution of manuals and the recording of rehabilitation videos. Understanding the psychological needs of mothers, discussing their feelings and experiences during pregnancy and childbirth, adopting narrative and reminiscence methods, using music, videos, photographs, and other materials to guide mothers to recall their past good experiences in life, the most unbeautiful work experiences, pleasant trips, my beloved relatives, and so on will help mothers build up their confidence in their future lives and cultivate a sense of responsibility, and enable them to positively cope with changes in their roles. Peer support work is organized with mothers who have good communication skills and have made a good transition to recovery, leading other mothers to learn about parenting and postnatal return to work measures. Maternal and child healthcare study manuals are distributed, and regular peer exchange and recreational activities are organized (such as shopping and watching movies) to gradually enable mothers to return to a normal life and divert their attention.

Positive thinking: Positive thinking, walking, meditation, yoga, and breathing training were combined with maternal recovery and emotional transformation. Initially, the medical staff investigated the maternal psychological state and influencing factors, led the maternal body scanning, positive thinking meditation, and positive thinking yoga through body scanning and meditation so that the mother could feel the present moment, accept the reality, and change its thinking mode; the nursing staff guided the maternal 3 min breathing exercises, lip-contracting respiration, abdominal respiration, and torso relaxation; and then to carry out positive thinking yoga, to learn the method of yoga, and to guide its; the nursing staff instructed the mothers to perform 3-minutes breathing exercises, lip-contraction breathing, abdominal breathing, and somatic relaxation.

Home-based rehabilitation care: A WeChat platform for mothers was created, called "Love Yourself", and mothers are required to join the group, send the knowledge of parenting skills, post-partum depression, post-partum exercise and rehabilitation, post-partum diet, observation of the incision after caesarean section, prevention of complications, and so on to the group by combining graphics and texts, and answering the problems encountered by mothers, combined with videos and online live broadcasts. Furthermore, the group provides rehabilitation exercises and healthy diets in combination with videos and online live broadcasts and tries to meet the reasonable needs of mothers as much as possible. Peer experience sharing is arranged once a week in the group, with women who have successfully recovered sharing their experiences of postnatal rehabilitation, precautions, and psychological experiences, setting an example to motivate them to actively learn relevant rehabilitation skills and pregnancy knowledge.

Response

The two groups were continuously intervened for 12 week every weekend through WeChat and telephone follow-up to investigate the implementation of the home rehabilitation plan after the discharge of the mother; to instruct the mother to recall today's mental thoughts, behaviors, and the completion of the rehabilitation program before going to bed every day; to learn about the problems in the process of rehabilitation by summarizing and reflecting on them and to make improvements.

Observation indicators

Depression level: Survey and assessment was conducted before and after nursing care using the Edinburgh Postnatal Depression Scale (EPDS)[7]; the scale involves 10 questions, each question is 0–3 points, with a total score of 30 points; if the score ≥ 13 points, there is the possibility of depression; the Hamilton Depression Scale (HAMD) contains 24 items[8], with outcomes of no depression, mild, moderate, and severe depression, respectively with 0–7, 8–19, 20–35, and > 35 points, respectively.

Mood state: The Brief Mood State Scale[9] was used before and after care, involving tension-anxiety (9 items, 0–36 points), depression-frustration (15 items, 0–60 points), anger-hostility (12 items, 0–48 points), fatigue-sluggishness (7 items, 0–28 points), confusion (7 items, 0–28 points), and energy-vigor (8 items, 0–32 points); the higher the score, the more.

Coping styles: Surveys were conducted before and after nursing care and evaluated using the Medical Coping Style Questionnaire[10], a 20-item scale with each item counting 1–4 points: patients faced (8 items, 8–32 points), avoided (7 items, 7–28 points), and succumbed (5 items, 5–20 points) dimensions; the higher the score for each dimension, the more the individual tends to that type of coping style.

Statistical methods

Data within the study were statistically analyzed using SPSS version 26.0. Measured data were expressed in the form of (mean \pm SD), meeting the normal distribution, the test of inter-group and intra-group data with independent and paired samples *t*, respectively; not meeting the normal distribution, expressed in the form of the median or for the interquartile spacing, the test of intra-group and inter-group data with paired and sample rank sum, respectively; count data were the rate (%), χ^2 test; $P < 0.05$ for the difference was statistically significant.

RESULTS

Before care, there was no significant difference in depression scores between the groups ($P > 0.05$); after care, depression scores were reduced between the groups, and EPDS and HAMD scores were lower in the observation group ($P < 0.05$; Table 2).

State of mind

Before nursing, there was no significant difference in the state of mind scores between the groups ($P > 0.05$), after which the state of mind between the groups improved; the observation group had the best degree of improvement ($P < 0.05$; Table 3).

Level of coping

Before care, coping with the disease was compared between the groups ($P > 0.05$), after which coping improved in all groups, with the observation group showing the best level of improvement ($P < 0.05$; Table 4).

Table 2 Comparison of depression scores between the two groups (score, mean ± SD)				
Group	EPDS		HAMD	
	Before	After	Before	After
Observation (<i>n</i> = 40)	17.13 ± 2.18	8.14 ± 1.67	21.15 ± 4.28	11.48 ± 2.48
Control (<i>n</i> = 40)	16.92 ± 2.25	11.08 ± 1.95	20.96 ± 4.35	15.83 ± 3.16
<i>t</i> value	0.348	5.950	0.162	5.627
<i>P</i> value	0.729	< 0.001	0.872	< 0.001

EPDS: Edinburgh Postnatal Depression Scale; HAMD: Hamilton Depression Scale.

Table 3 Comparison of mindfulness scores between groups (score, mean ± SD)												
Group	Nervousness-anxiety		Depression-frustration		Anger-hostility		Tiredness-slowness		Bewilderment-confusion		Energy-vigor	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Observation (<i>n</i> = 40)	21.04 ± 3.89	8.14 ± 1.8 ^a	40.25 ± 4.84	13.52 ± 2.4 ^a	19.02 ± 2.87	6.15 ± 1.5 ^a	15.05 ± 2.08	5.24 ± 1.28 ^a	16.38 ± 2.15	6.89 ± 1.3 ^a	9.08 ± 3.14	17.52 ± 1.6 ^a
Control (<i>n</i> = 40)	20.96 ± 3.94	11.69 ± 1.9 ^a	39.81 ± 4.96	16.98 ± 2.5 ^a	18.73 ± 3.01	8.98 ± 1.6 ^a	14.92 ± 2.12	7.18 ± 1.35 ^a	16.10 ± 2.25	8.52 ± 1.4 ^a	8.89 ± 3.20	13.24 ± 1.8 ^a
<i>t</i> value	0.091	8.417	0.402	6.127	0.441	7.926	0.277	6.595	0.569	5.144	0.268	4.382
<i>P</i> value	0.927	< 0.001	0.689	< 0.001	0.660	< 0.001	0.783	< 0.001	0.571	< 0.001	0.789	< 0.001

^a*P* < 0.05 comparison with pre-care data between groups.

Table 4 Comparison of coping with illness between groups (score, mean ± SD)						
Group	Face-to-face		Circumvent		Surrender	
	Before	After	Before	After	Before	After
Observation (<i>n</i> = 40)	15.95 ± 3.18	26.48 ± 3.35 ^a	19.12 ± 2.48	12.08 ± 2.50 ^a	12.04 ± 2.68	8.14 ± 1.15 ^a
Control (<i>n</i> = 40)	16.20 ± 3.25	21.73 ± 3.20 ^a	18.92 ± 2.51	15.75 ± 2.69 ^a	11.92 ± 2.75	9.95 ± 1.20 ^a
<i>t</i> value	0.348	6.485	0.358	6.321	0.198	6.887
<i>P</i> value	0.729	< 0.001	0.721	< 0.001	0.844	< 0.001

^a*P* < 0.05 comparison with pre-care data between groups.

DISCUSSION

Postpartum depression is a common emotional problem that occurs specifically in women, mainly owing to endocrine and social factors, genetics, and adverse emotions during pregnancy[11]. Among them, cesarean section is the main mode of maternal delivery, with poor postpartum morphological recovery, destroyed physical integrity, lasting pain, long recovery time, and other conditions, that further affect the maternal psychological state, aggravating the degree of depression[12]. For postpartum depressed mothers, nursing intervention is the main solution. The SOR concept is a theoretical model for individual behavior caused by a variety of stimuli, and the stimulus is embodied in the individual's physiological and psychological factors, but also from external environmental factors, which produce a variety of behavioral motives[13]. Therefore, this study adopted the problem-solving nursing model under the guidance of the SOR theory, using the problem as the nursing orientation and combining the SOR theory with corresponding nursing interventions, which can standardize the nursing process and improve the level of clinical care.

This study showed that the EPDS and HAMD-24 item scores of the observation group were lower than those of the control group after nursing care (*P* < 0.05), indicating that the use of the problem-solving nursing model under the guidance of the SOR theory could alleviate the degree of maternal depression. There are few clinical reports about the effect of this kind of nursing program on postpartum depression; SOR theory is mainly used to analyze the psychology and behavior of consumers, and is gradually used in the analysis of social psychology. The use of the SOR theoretical

model can be accurately and effectively analyze the individual psychological and behavioral analysis of the period of the new coronary pneumonia changes[14]. Therefore, we can understand the psychological problems of mothers, and based on the SOR theory through the assessment of the problem, we can analyze the external stimulus factors, and conduct the corresponding nursing solutions in the cognitive and emotional domains to improve the level of nursing interventions, create a good family atmosphere, improve the relationship between the husband and the wife, improve their parenting skills, enrich their experience of parenting, and avoid the state of depression owing to the cognitive deficiencies and insufficient nursing care.

State of mind is an emotional state that affects all experiences and significantly influences an individual's life, work, mental state, and behavioral performance. Post-traumatic stress disorder arising after cesarean section may contribute to the development of postpartum depression[15], which directly affects an individual's state of mind. Early symptoms of postpartum depressed mothers were sadness, fatigue, feelings of neglect, lack of interest in the baby, decreased appetite, and sleep disturbances[16]. In this study, tension-anxiety, depression-frustration, anger-hostility, fatigue-sluggishness, and confusion-confusion were lower and energy vitality was higher in the observation group than in the control group after nursing care ($P < 0.05$). The results indicate that the use of the problem-solving nursing model guided by SOR theory can improve the maternal state of mind. Through problem assessment and external stimulus analysis, intervention, combined with maternal disease characteristics and clinical information, the common problems in the process of maternal recovery were analyzed, and the mothers and husbands were helped to establish a correct view of childbearing; and to create a relaxing and pleasant family atmosphere to reduce the impact of external stimuli on the mothers, and to encourage the mothers to participate in more recreational activities, participate in the work, and so on. This alleviates the mothers' psychological and physiological burdens and strengthens the maternal psychological care to help establish the maternal state of mind. At the same time, strengthening maternal psychological care, helping mothers build confidence in their future lives, cultivating their sense of responsibility, and playing the role of role models to motivate mothers to form positive behaviors can reduce the state of maternal depression; through the connection of positive thoughts, breathing, body sensation, and observation of awareness, other methods can divert the attention of the mothers to alleviate the negative state of mind and to regulate the emotional state of the mothers[17].

Individuals can face stressful events and environments to resist negative emotions and avoid avoidance or withdrawal. The study showed that the level of coping with illness was significantly higher in the observation group than in the control group after care, indicating that the problem-solving nursing model guided by the SOR theory improves the level of maternal coping with illness[18]. This nursing programme strengthen the husband and wife's health management by coordinating the role of the husband to undertake household activities, and do a good job of husband and wife's parenting skills training, which can improve the maternal and husband's knowledge of the disease mastery level, and after discharge from the hospital through the WeChat platform to push the maternal postnatal rehabilitation exercise, healthy diet and other knowledge, to promote the maternal actively learn the relevant rehabilitation skills, and cope with postnatal depression. Furthermore, the positive thinking exercises can increase maternal coping with the disease level. These exercises were divided into 3-min breathing exercises and ice-holding exercises, which enabled the mothers to gradually complete the psychological state of acceptance, trust, and inaction to face the present, guide them to face and accept the disease directly, lower their perceptual pressure, and improve their coping with the disease.

In the future, we also need to increase the sample size by a certain amount in order to avoid limitations such as study design and potential confounders, which will strengthen the credibility of the study, and further research could enhance the generalisability of the findings and provide deeper insights into the mechanisms behind the observed effects.

CONCLUSION

Adopting the problem-solving nursing model guided by the SOR theory for postpartum depressed mothers after cesarean delivery can significantly reduce the degree of maternal depression, improve their state of mind, reduce maternal tension-anxiety, depression-frustration, anger-hostility, and fatigue-sluggishness negative state of mind, increase their energy-vitality level, and improve their coping level with illness, which can be an ideal care method for postpartum depressed mothers.

FOOTNOTES

Author contributions: Yuan RF and Jiang MQ designed the research study; Yuan RF, Jiang MQ, Li J, Zhang JJ performed the research; Yuan RF, Jiang MQ, Li J, Zhang JJ contributed new reagents and analytical tools; Yuan RF and Jiang MQ analyzed the data and wrote the manuscript. All authors have read and approved the final version of the manuscript. Two co-first authors (Yuan RF, and Jiang MQ) and two co-correspondents (Li J and Zhang JJ) made equal contributions for several reasons: Equal research work: Yuan RF, and Jiang MQ undertake the work of equal importance and workload in the research project. Similar professional knowledge contribution: They each relied on their professional knowledge and contributed the same amount of strength to the success of the research; Cooperation and collaboration: In the entire research process, Yuan RF, and Jiang MQ presented close cooperation and collaboration, and jointly promoted the progress of the research; In the dimension of research design and planning, Li J and Zhang JJ jointly participated in the formulation of the research plan, including the clarification of research objectives, the selection of methods, and the design of the experimental process. They jointly discussed and determined the most suitable research plan. As for data collection and analysis, the two equally undertake the task of collecting data to ensure the accuracy and integrity of the data. During the data analysis, they jointly interpreted the data to ensure the reliability of the results; In the stage of result interpretation and discussion, Yuan RF and Jiang MQ participated in the interpretation and discussion of the results together, and deeply explored the meaning and impact of the research

findings. In the process of writing and revising the paper, they worked together and carefully wrote each section of the paper. Li J and Zhang JJ also participated in it, providing valuable opinions and suggestions, and jointly improved the content and structure of the paper.

Institutional review board statement: The study was reviewed and approved by the (Jiangyin People's Hospital) Institutional Review Board.

Clinical trial registration statement: The study was registered at the Clinical Trial Center with registration number: researchregistry10266.

Informed consent statement: All study participants and their legal guardians provide informed written consent before the study recruitment.

Conflict-of-interest statement: Dr. Li has nothing to disclose.

Data sharing statement: No additional data are available.

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

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S-Editor: Lin C

L-Editor: A

P-Editor: Che XX

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This pain drives me crazy: Psychiatric symptoms in women with interstitial cystitis/bladder pain syndrome

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Specialty type: Psychiatry

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade C

Creativity or Innovation: Grade C

Scientific Significance: Grade B

P-Reviewer: Yu RQ, China

Received: February 28, 2024

Revised: April 22, 2024

Accepted: May 7, 2024

Published online: June 19, 2024

Processing time: 112 Days and 1.8 Hours



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Abstract

BACKGROUND

Interstitial cystitis/bladder pain syndrome (IC/BPS) is an at least 6-mo noninfectious bladder inflammation of unknown origin characterized by chronic suprapubic, abdominal, and/or pelvic pain. Although the term cystitis suggests an inflammatory or infectious origin, no definite cause has been identified. It occurs in both sexes, but women are twice as much affected.

AIM

To systematically review evidence of psychiatric/psychological changes in persons with IC/BPS.

METHODS

Hypothesizing that particular psychological characteristics could underpin IC/BPS, we investigated in three databases the presence of psychiatric symptoms and/or disorders and/or psychological characteristics in patients with IC/BPS using the following strategy: ("interstitial cystitis" OR "bladder pain syndrome") AND ("mood disorder" OR depressive OR antidepressant OR depression OR depressed OR hyperthymic OR mania OR manic OR rapid cycl^{asterisk} OR dysthymi^{asterisk} OR dysphori^{asterisk}).

RESULTS

On September 27, 2023, the PubMed search produced 223 articles, CINAHL 62, and the combined PsycLIT/PsycARTICLES/PsycINFO/Psychology and Behavioral Sciences Collection search 36. Search on ClinicalTrials.gov produced 14 studies, of which none had available data. Eligible were peer-reviewed articles reporting psychiatric/psychological symptoms in patients with IC/BPS, *i.e.* 63 articles spanning from 2000 to October 2023. These studies identified depression and anxiety problems in the IC/BPS population, along with sleep problems and the tendency to catastrophizing.

CONCLUSION

Psychotherapies targeting catastrophizing and life stress emotional awareness and expression reduced perceived pain in women with IC/BPS. Such concepts should be considered when implementing treatments aimed at reducing IC/BPS-related pain.

Key Words: Interstitial cystitis/bladder pain syndrome; Psychiatric symptoms; Psychological symptoms; Catastrophizing; Anxiety; Depression

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Core Tip: Interstitial cystitis/bladder pain syndrome (IC/BPS) occurs in 2%-18% of the general population, most commonly in women and in people having first-degree relatives affected by the same syndrome. Despite its name suggesting that an inflammation could be involved, no inflammatory aetiology has been found to date. The syndrome causes major sufferance in affected patients and may even affect their psychological status. In spite of efforts to resolve it, no treatment currently exists. Catastrophizing is all too often present in pain syndromes and may be targeted by psychotherapy to reduce the impact of IC/BPS in affected people.

Citation: Mazza M, Margoni S, Mandracchia G, Donofrio G, Fischetti A, Kotzalidis GD, Marano G, Simonetti A, Janiri D, Moccia L, Marcelli I, Sfratta G, De Berardis D, Ferrara O, Bernardi E, Restaino A, Lisci FM, D'Onofrio AM, Brisi C, Grisoni F, Calderoni C, Ciliberto M, Brugnami A, Rossi S, Spera MC, De Masi V, Marzo EM, Abate F, Boggio G, Anesini MB, Falsini C, Quintano A, Torresi A, Milintenda M, Bartolucci G, Biscosi M, Ruggiero S, Lo Giudice L, Mastroeni G, Benini E, Di Benedetto L, Caso R, Pesaresi F, Traccis F, Onori L, Chisari L, Monacelli L, Acanfora M, Gaetani E, Marturano M, Barbonetti S, Specogna E, Bardi F, De Chiara E, Stella G, Zanzarri A, Tavoletta F, Crupi A, Battisti G, Monti L, Camardese G, Chieffo D, Gasbarrini A, Scambia G, Sani G. This pain drives me crazy: Psychiatric symptoms in women with interstitial cystitis/bladder pain syndrome. *World J Psychiatry* 2024; 14(6): 954-984

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/954.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.954>

INTRODUCTION

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic (lasting 6 mo or more) non-infectious bladder inflammation of unknown origin. The cardinal symptom is chronic suprapubic, abdominal, and/or pelvic pain. At the same time, patients may show pollakiuria, nocturia, urinary urgency, and dyspareunia[1]. Alterations in the sexual, behavioural, cognitive, and emotional domains are not uncommon[2]. Furthermore, after diagnosis, patients with IC/BPS are commonly untreated or treated for more than two-thirds of cases with drugs lacking approval from official agencies [3], thus increasing the occurrence of comorbidities and amplifying its healthcare costs.

The epidemiological data reported in the literature are partly inaccurate due to a high misdiagnosis rate. However, IC/BPS seems to affect 20% of women, while being quite uncommon between men[3].

Since the aetiopathogenesis of IC/BPS is little known, its diagnosis is difficult to make and the therapeutic options are limited. Its pathophysiology is believed to involve pelvic wall defects with increased permeability of the transitional epithelium to urinary toxins and consequent transmural inflammation[1]. The initial trigger may be infectious (*Proteus mirabilis*, *Klebsiella pneumoniae*, *Citrobacter*, *Enterobacter*, *Pseudomonas*, *Enterococcus faecalis*, *Staphylococcus saprophyticus*, and group B streptococci, but most of all *Escherichia coli*[4]) or not, and may induce aberrant immune and inflammatory responses[5]. These may result in increased production, activation and degranulation of mast cells and eosinophils, and the subsequent release of histamine and proinflammatory cytokines may ensue in inflammation, consequent vasodilation, sensory nerve stimulation and eventually, tissue damage[5]. Neurogenic inflammation and nerve fibre proliferation, with nerve hyperstimulation and sensory abnormalities[1,6,7] and recurrent urinary infections[1] may also concur. Finally, IC/BPS has been associated with early emotional trauma and hyperactivation of the stress axis[2].

The pelvic diaphragm has an extremely complex innervation that includes several neurological pathways, the function of which has not been elucidated. It is probable that this very intricate innervation is under the control of higher centres; in fact, psychological and emotional factors affect profoundly the function of the pelvic floor. It could be that pelvic organs cross-sensitize in response to earlier threat or traumatic events, prompting some investigators to add a bladder component to the brain-gut axis (including the microbiome) and speak about the bladder-gut-brain axis[8]. This cross-sensitization could result in perceived conjoint bladder- and gut-related emotional distress.

Psychosocial factors, like comorbid anxiety and depression, low quality of life, and trauma-related symptoms accompany and intensify the illness[9,10]. While psychosocial factors influence the development of chronic pain[11], unaddressed psychosocial elements of chronic pain can in turn shape patient perceptions and behaviour, often leading to symptom persistence through central sensitization[12] and are associated with poorer functioning, adjustment, prognosis, and response to treatment[12]. These findings suggest not only a strong association, but also that psychosocial symptoms and bladder-specific symptoms reinforce one another bi-directionally.

In addition, the perception of pain and its chronicity may be modified by emotional and cognitive factors[13]. Increasing evidence suggests that the tendency to magnify the threat value of the pain stimulus, the sense of helplessness in the face of pain, and the inability to inhibit pain-related thoughts, which together constitute the psychic phenomenon known as pain catastrophizing (PC), are associated with the activation of brain regions implicated in processing the affective dimensions of pain but also in cognitive regulation of emotion and cognition, such as the anterior cingulate cortex and ventromedial and dorsolateral prefrontal cortices and can lead to aberrant hypothalamic-pituitary-adrenal axis activity and altered cytokine responses to pain[14], thus resulting in maladaptive plastic changes responsible for the maintenance of chronic pain[13]. Since chronic pain is the cardinal symptom of IC/BPS, these processes could be involved in the pathophysiology of the disorder. Therefore, careful assessment of pain and PC should be included in the clinical workup of IC. In fact, PC was shown to be present in IC/BPS and constitute a core factor[15,16] with a bidirectional relationship[17], with its effect on IC/BPS being mediated by other psychological factors[18].

From this perspective, the poor outcomes in terms of therapeutic efficacy could be traced to inadequate care-taking[19] that underestimates psychological factors and concomitant psychiatric disturbances[20].

The aim of this review was to identify psychological and mental symptoms in IC and chronic bladder pain to underline the urgent need for integration of psychological assessment and management into care plans for IC/CBP.

MATERIALS AND METHODS

To identify studies dealing with the presence of psychiatric/psychological symptoms in patients with the IC/BPS, we investigated the PubMed, CINAHL and PsycLIT/PsycARTICLES/PsycINFO/Psychology and Behavioral Sciences Collection databases on November 7, 2023. We also used the ClinicalTrials.gov site to identify ongoing studies, using the following strategy: Condition/disease: Interstitial cystitis; Other terms: Psychological symptoms; Intervention/treatment: blank. To be included, studies had to be original and reporting the proportion of psychiatric disorders or symptoms or psychological symptoms in patients with IC/BPS. Articles ought to be published after a peer reviewing process, to explicitly provide data for psychiatric or psychological symptoms, include patients with IC/BPS and quantify their psychiatric or psychological symptoms as a group, not lumping their data along with data of patients with other conditions (in such case, studies were excluded and labelled as “no IC/BPS” and added to the studies that did not include patients with IC/BPS), nor reporting impressions with no clear data (in such case they were excluded as “no data”). When studies referred to the same sample or to an increased sample including previously analysed patients, only the study with more data (or more complete analyses) was included, with the others excluded as “overlapping” samples. Further exclusion criteria were not reporting psychiatric or psychological symptoms, labelled as “nopsys”, a design focused on other outcomes (labelled “off-target”, which comprised both studies with an inadequate design as referred to our aims, and unfocused papers with outcomes different from those we investigated), being not related to the subject matter (“unrelated”), surveys of treating physicians or the lay public containing their opinions than data of patients (*i.e.* the sample was not composed of patients, but consisted of physicians or people interviewed by the survey promoters, labelled as “survey”), other opinion papers without data, such as editorials or letters to the editor or hypotheses and qualitative studies without precise figures as to emerged themes, labelled as “opinion”, animal or *in vitro* studies (preclinical), labelled as “animal”, protocols of future researches with not even preliminary data, labelled as “protocol”, reviews and meta-analyses, labelled as “review” (but their reference lists were hand-searched to identify possibly eligible studies that eluded our search strategies), and obviously duplicates or corrections of a published paper already existing in a given database; overlapping records between databases were also labelled as “duplicates”.

Our search strategy was (“interstitial cystitis” OR “bladder pain syndrome”) AND (“mood disorder” OR depressive OR antidepressant OR depression OR depressed OR hyperthymic OR mania OR manic OR rapid cycl* OR dysthymi OR dysphori) for all databases and was carried out on November 7, 2023.

To decide eligibility of a given study, we performed Delphi rounds among all authors until complete consensus was reached. Not more than three were necessary for all articles. We conducted this systematic review adopting the PRISMA statement[21]. Detailed results of databases searching, PRISMA checklist and flowchart are shown in the Supplement. Overall judgments for each rated study and comments are shown in the online Supplement (Supplementary Table 1). We did not register our review on PROSPERO. The articles resulting from our search are shown in the Supplement, along with inclusion/exclusion decisions and the reasons for the latter. The selection process is depicted in Figure 1, which shows the PRISMA flowchart. Risk of Bias (RoB) was assessed through the Cochrane RoB method as described in the Cochrane Handbook[22].

RESULTS

Our search on November 7, 2023 yielded 224 records on PubMed, 62 on CINAHL, and 36 on PsycLIT/PsycARTICLES/PsycINFO/Psychology and Behavioral Sciences Collection, and 1 added from other sources, for a total of 323 records, 67 of which were duplicates and immediately removed. The inclusion process is depicted in Supplementary Table 1. Records identified by the search strategy spanned from March 1988 to October 25, 2023, with eligible records ranging from July 2000 to October 2023. There were 63 records identified as eligible; they are summarised in Table 1[23-85]. These studies were longitudinal ($n = 29$) or cross-sectional ($n = 34$). There were some studies conducted with the same sample, but they focused on different outcomes, so we retained them all[35,36,49,54,55,60,70] (Table 1).

The search conducted on the ClinicalTrials.gov site provided 14 trials. Of them, 9 were interventional and 5 observational (Table 2). Ten were completed, one was recruiting, one was not yet recruiting, and two had an unknown status. None had data to provide or publications related with their data. However, three of them had received publication by the above date (one in a preprint, not peer-reviewed, Table 2).

Figure 2 shows the distribution of included studies across time. An increase can be noted from early to recent years, which is not steady, but rather fluctuating. However, the 17-year 2000-2016 period provided 29 studies, less than those of the 7-year 2017-2023 period ($n = 34$).

Studies were scattered though many sites worldwide, although most of them are concentrated in the United States-North America. Among the 14 ongoing or unpublished studies in the ClinicalTrials.gov database, 9 are in the United States and the United States participates in another multinational study (United Kingdom, Portugal, Germany, and Denmark). The other studies in this database are two Italian, one Turkish, and one Israeli. Among eligible studies, 31 were performed in the United States alone, two were performed conjointly with Canada, three were international studies involving Canada, Denmark, and India, while five were Canadian only studies, eleven Chinese, two French, two South Korean, two Italian, one each German, Turkish, Russian, and Dutch and one was “international” (unspecified where from, but data processed in Philadelphia, PA, United States). Surprisingly, no eligible study was based in Australia-New Zealand, and no study came from Africa, presumably for economic reasons.

Initially, most studies were single-site, prevalently cross-sectional[23-26], and regarded patients seen vis-à-vis; later, from 2008 on, there started international collaborations and multicentre studies[39,40,46,72], and those accessing

Table 1 Summary of studies investigating psychiatric symptoms in interstitial cystitis¹

Ref.	Population	Design	Psychiatric symptoms	Conclusions/observations
Rabin <i>et al</i> [23], 2000	80 females, treated for IC, aged 16-75 yr (mean age = 44.6 ± 12.4 yr)	CS. Questionnaires and scales administered included Demographics; General Questionnaire; Disability; ICES; Pain Scale; Self-Stigmatization Scale; CES-D	52.6% of IC sample reported dep sym; levels of dep experienced by IC pts are > than general population/other chronic pain populations; regression showed dep to be associated with self-efficacy for male aging pain ($P < 0.01$), self-stigmatization ($P < 0.05$), and pain ($P < 0.05$)	Females with IC reported physical and emotional burden and showed ↑ dep levels
Rothrock <i>et al</i> [24], 2002	65 female pts 22 to 81 yr (mean age ± SD: 51.0 ± 16.1) with IC + 40 HC 25-82 yr (mean age 52.6 ± 15.8)	CS. Administered scales comprised BDI; MOS SF-36; HAM-D	Pts reported significantly poorer QoL than HC across all MOS domains, including emotional difficulty, and mental health ($P < 0.01$). Pts reported > dep sym on the BDI than HCs (95%CI: 4.1-7.1 vs 1.5-4.9, $P < 0.05$), as well as on the HAM-D (95%CI: 6.1-9.6 vs 0.7-2.3, $P < 0.001$). In pts, mean HAM-D score was 7.9-6.8 (range 0-25), indicating mild dep sym. Only 10.2% of pts scored in the moderate-to-severe range of dep sym on the HAM-D	A diagnosis of IC is related to poorer functioning in various life domains. ↑ sym severity related to poorer physical/social functioning and mental health
Rothrock <i>et al</i> [25], 2003	64 female pts with IC	CS. Scales administered included questionnaires assessing QoL, coping and symptoms; HAM-D	Pts coping with greater catastrophising reported ↑ impairments in dep sym, general mental health, social functioning, vitality, and ↑ pain. Seeking social support was associated with ↓ dep sym	Maladaptive coping strategies are associated with ↑ levels of dep sym and ↓ QoL in pts with this condition. Psychosocial interventions aimed at ↑ adaptive coping may positively impact IC
Novi <i>et al</i> [26], 2005	46 females with IC+ 46 HC	CS. 46 females with IC and 46 HC were evaluated by PHQ-9 DM (MD defined as a score ≥ 10); RIISQ to find out the diagnosis of IBS	Compared with HC, IC pts were more likely to be diagnosed with IBS (OR 11, 95%CI: 2.7-52, $P < 0.001$) and dep (OR 3.97, 95%CI: 1.17-14.1, $P < 0.05$)	The association of IBS and dep appears to be > in females with IC
Wu <i>et al</i> [27], 2006	749 pts with IC and < 65 yr + HC (646 females and 103 male)	Lo. Costs incurred in the 1 st yr after IC diagnosis and co-morbidities were compared between IC pts and HC. A multivariate two-part model was applied to estimate the IC direct medical cost, indirect cost and total cost to adjust for observed pts demographics and comorbidities. Statistical significance was evaluated by the bootstrap method	IC pts had 130% higher direct costs ($P < 0.05$) and 84% higher indirect costs than HC. IC pts also had a higher diagnostic prevalence of prostatitis (RR = 40.0), endometriosis (RR = 7.4), vulvodynia (RR = 6.9), chronic pelvic pain (RR = 5.8) and urinary tract infections (RR = 5.1; all $P < 0.05$). IC pts were also more likely to report dep (RR = 2.8) and anx (RR = 4.5) than HCs (all $P < 0.05$)	IC is a costly disease associated with co-morbidities. More accurate diagnosis and earlier and more appropriate treatment of IC would lead to better management of co-morbidities and ↓ healthcare costs
Fan <i>et al</i> [28], 2008	47 IC pts (38 females and 9 male) +31 HC	CS. 47 IC pts and a group of 31 age-matched, asymptomatic females received HAM-D and HRSA. IC pts also completed questionnaires relating to IC symptom severity, including urgency and frequency and O'Leary Sant index	Mean dep scores = 16.6. 15 pts (31.9%) with mild dep symptoms, 5 (10.6%) mild-to-moderate and 20 (42.6%) moderate-to-severe dep. mean anx score = 21.0, with 21 (44.7%), 9 (19.1%) and 17 (36.2%) pts displaying mild, mild-to-moderate, and moderate-to-severe anx symptoms, respectively. Pain scale and O'Leary Sant index were significantly correlated to anx and dep score	Most of IC pts feature significant dep and anx (85% of IC pts featured significant affective symptoms). The extent of affective symptoms would appear to correlate well with IC symptom severity
Clemens <i>et al</i> [29], 2008	239 IC female pts and 717 matched HC (1:3 ratio)	Lo (case-control). A computer search of the administrative database at Kaiser Permanente Northwest, Portland, Oregon was performed for 1 May, 1998 to 30 April, 2003. All females with a medical record diagnosis of IC (ICD-9 code 595.1) were identified. These cases were matched with 3 controls each based on age and duration in the health plan. Assigned ICD-9 diagnoses to these 2 groups were compared	239 cases and 717 matched controls were analysed. 23 diagnoses were significantly > in IC pts than in HC ($P = 0.005$): 7/23 were other urological or gynaecological. Additional specific conditions associated with IC were gastritis (OR 12.2), child abuse (OR 9.3), FM (OR 3.0), anx disorder (OR 2.8), headache (OR 2.5), oesophageal reflux (OR 2.2), unspecified back disorder (OR 2.2) and dep (OR 2.0)	IC was associated with multiple other unexplained physical symptoms and certain psychiatric conditions. The possible biological explanations for these associations remain to be established

		using ORs		
Clemens <i>et al</i> [30], 2008	174 male pts with chronic prostatitis/CPPS (mean age = 52) and 72 male, age-matched HC. 111 female pts with interstitial cystitis/PBS (mean age = 50) and 175 females, age-matched HCs	Lo (case-control). Pts and HC were analysed. Demographic information, current medication use, medical history was collected; NIH-CPSI for male subjects, and the ICSI and ICPI for females; PHQ used to assess mental health	Mental health disorders were identified in 13% of the chronic prostatitis/CPPS cases and 4% of male HC (OR 2.0, $P = 0.04$), as well as in 23% of IC/PBS cases and 3% of females HCs (OR 8.2, $P < 0.0001$). Disease status (case <i>vs</i> control) (OR 10.4, $P = 0.001$) and income > 50000 USD (OR 0.34, $P = 0.008$) were the only 2 variables independently predictive of the presence of a mental health diagnosis. Medications for anx, dep or stress were taken by 18% of pts with chronic prostatitis/CPPS, 37% of those with IC/PBS, 7% of male HCs and 13% of females HCs	Dep and PA are ↑ in male and females with pelvic pain conditions than in HCs. Furthermore, anx and dep may be more difficult to treat in pts with urological pain syndromes than in HCs
Goldstein <i>et al</i> [31], 2008	141 females diagnosed with IC (mean age = 45.9 yr)	CS. Prevalence of dep was measured using the BDI-II; Prevalence of abuse was evaluated using the validated DAQ	98 (70%) pts scored ≥ 14 on the BDI-II. The mean score of the total sample was 14.6 (SD 9.2), representing mild dep. Of all of those that scored in the dep range (≥ 14), the mean score was 22.4 (SD 6.4) representing moderate dep. The prevalence of sexual abuse from validated questionnaires was 36%; the prevalence of childhood sexual abuse was 21%; physical abuse was 31%	Pts with IC had > prevalence of dep and sexual abuse than the general population. Females with IC should be screened for dep and abuse and referred to a mental health expert as necessary for treatment
Kim and Heitkemper[32], 2009	298 females (mean age = 74.3 ± 6.20)	Lo. To estimate the prevalence of IC/PBS symptoms and describe the relationships among symptoms, general sample characteristics, dep and QOL in older Korean females → ICSI/ICPI, KGDS, HRQOL, KHQ. Statistical analysis → SPSS/WIN 15.0 program; prevalence/urologic characteristics → freq, mean, and severity; correlations among demographic characteristics. ICSI-K and ICPI-K, KGDS, and KHQ → Pearson; group differences in variables by ICSI-K cut-off score 5 → ANOVA	The prevalence of mild to severe IC symptoms using ICSI-K was 54%. The percentage at risk for IC using summed scores of ICSI-K and ICPI-K was 43.6%. The ICSI-K scores had moderate correlations with KHQ and had mild correlations with KGDS; The ICPI had strong positive correlations with KHQ and had mild correlations with KGDS. KHQ scores had mild positive correlation with KGDS	Almost half of older Korean females in this sample had IC/PBS symptoms using IC/PBS cut-off score of 5. IC symptoms and problems impacted limitation in life highly
Tsai <i>et al</i> [33], 2010	69 IC pts [mean age = 42.0 ± 16.3 (range: 20–79 yr)], 52 females (mean age = 44.2 ± 16.0 yr), 17 males (mean age = 35.2 ± 15.6 yr); $P < 0.05$	CS. PSQI and HADS were used to evaluate quality of sleep and dep level, respectively. Multiple linear regressions were used to identify independent factors of sleep quality	Mean PSQI global score was 9.5 ± 4.2 (range: 1–19); 81.2% of pts had poor sleep quality (PSQI > 5). Regression analysis suggested that IC severity (β coefficient = 0.42, $P < 0.001$) and level of anx and dep (β coefficient = 0.26, $P < 0.05$) were significant independent risk factors for poor sleep quality	Poor sleep quality is common in IC pts and severity of urological symptoms and dep levels are important independent risk factors
Giannantoni <i>et al</i> [34], 2010	14 female pts with IC	Lo. Controlled-trial. 14 pts received 1 BoNT/A inj under cystoscopic guidance. At pre- and 3 mo post- treatment all pts underwent urological assessment, VAS, HAM-A, HAM-D and SF-36 to assess QoL	At pre-treatment all 14 pts had ↑ daytime and nighttime urinary frequency and ↑ VAS scores. 9 pts had pathological HAM-A and HAM-D scores. At the 3-mo fup 10/14 pts reported a subjective improvement in pain. Mean VAS score, mean daytime and nighttime urinary frequency ↓ ($P < 0.01$, $P < 0.01$ and $P < 0.01$). All SF-36 and HAM-A domains significantly improved ($P < 0.01$). All HAM-D domains, except weight and sleep disorders, significantly improved, particularly somatoform syms ($P < 0.01$), cognitive performance ($P < 0.01$), and circadian variations ($P < 0.01$)	In pts with refractory PBS with symptoms of anx, dep and poor QoL, BoNT/A intravesical treatment reduced BPS, improved psychological functioning, and well-being
Bogart <i>et al</i> [35], 2011	1469 females who met criteria for BPS/IC	CS. A telephone screening of 146,231 households and	Of those with a current sexual partner (75%), 88% reported general	Females with BPS/IC symptoms experience very high levels of sexual

		telephone interviews with females with BPS/IC symptoms were conducted. Health-related QoL was measured using the Short-Form 36-item Health Survey physical health scale; The Patient Health Questionnaire-8 items was used to assess dep symptoms; females who had a current partner were asked the number of times they had engaged in vaginal sex in the past year and the extent to which they experienced the 6 BPS/IC-specific sexual dysfunction symptoms and 5 general sexual dysfunction symptoms in the past 4 wk	sexual dysfunction symptom and 90% reported BPS/IC-specific sexual dysfunction symptom in the past 4 wk. In the multivariate models, BPS/IC-specific sexual dysfunction was significantly associated with more severe BPS/IC symptoms, younger age, worse depression symptoms, and worse perceived general health	dysfunction and higher level of dep
Watkins <i>et al</i> [36], 2011	1469 females who met criteria for BPS/IC	CS. A telephone screening of 146,231 households and telephone interviews with females with BPS/IC symptoms. A weighted probability sample of 1469 females who met BPS/IC criteria was identified. Measures of BPS/IC severity, dep symptoms, PA, and treatment utilization were administered. <i>T</i> and χ^2 tests used to examine differences between groups	> 1/3 of the sample (<i>n</i> = 536) had a probable diagnosis of dep, and 52% (<i>n</i> = 776) reported recent PA. females with a probable diagnosis of dep or current PA reported worse functioning and ↑ pain and were less likely to work	Rates of probable current dep and PA are high, and there is considerable unmet need for treatment
Moskovenko[37], 2011	112 female pts with IC	CS. Clinical evaluation	↑ Neuroticism in 74 (66.1%) cases, moderate or high-reactive anxiety in 98 (87.5%), high personal anxiety in 36 (32.1%); 8.0% pts had depressive disorders > moderate	Pts with IC have higher odds for having psychoemotional disturbances
Peters <i>et al</i> [38], 2011	639 females: 425 HC(s), 36 with ulcerative IC/PBS (ULC) and 178 non-ulcerative IC/PBS (N-ULC)	CS. females with IC/PBS and HC(s) completed a mailed survey assessing for 21 diagnoses. IC/PBS subtype was determined by hydrodistention reports. Standardized questionnaires assessed IC/PBS symptoms (ICSI-PI) and for undiagnosed fibromyalgia, IBS, and dep (SIS; Rome III Functional Bowel Questionnaire; CES-D). Data were analysed using the Pearson chi-square, Fisher exact, Wilcoxon rank test, or Spearman rank correlation coefficient	ULC IC/PBS pts were older (median 63 yr; <i>P</i> < 0.01) and less employed (<i>P</i> < 0.01), but groups were similar on other demographic characteristics. N-ULC reported more chronic diagnoses (mean 3.5 ± 2.3) than ULC (2.3 ± 2.0) and controls (1.2 ± 1.5; <i>P</i> < 0.01). When N-ULC and ULC IC/PBS patients were compared, more N-ULC IC/PBS patients had fibromyalgia (<i>P</i> = 0.03), migraines (<i>P</i> = 0.03), temporomandibular joint disorder (<i>P</i> < 0.01), and higher CES-D (<i>P</i> = 0.02) and SIS scores (<i>P</i> = 0.01). The ULC IC/PBS group voided more frequently during the daytime (<i>P</i> = 0.03) and nighttime (<i>P</i> < 0.01) and had smaller mean bladder capacity than N-ULC (<i>P</i> < 0.01). No significant differences were seen between N-ULC and ULC IC/PBS patients on the ICSI-PI and Rome III	Notable differences in the number of comorbid diagnoses and symptoms were seen between IC/PBS subtypes and controls
Panzer <i>et al</i> [39], 2011	407 females with IC	Lo. All participants were asked to complete PSQI and ICSI/ICPI	Mean global PSQI score = 13.12 (SD ± 3.61) with all pts reporting a score of 6 or above. Results from the hierarchical multiple regression revealed that after controlling for age, menstrual status, years with IC, and dep, the 4 symptom predictors of IC (pain, urinary frequency, urinary urgency, and nocturia) alone explained 21% of the variance ($F_{(4, 398)} = 8.41$, <i>P</i> < 0.001) in sleep quality. Only pain, nocturia, and urinary urgency contributed significantly (<i>P</i> < 0.05)	Females with IC have disrupted sleep and poor subjective sleep quality. Predominant symptoms of IC related to poor sleep include nocturia and pain
Nickel <i>et al</i> [40], 2011	207 IC/BPS female pts and 117 HC matched for age, partner status	Lo (case-control). All participants were asked to complete the CTES, the ICSI,	Before 17 yr of age, the IC/BPS cases reported > prevalence of "raped or molested" compared to HCs (24.0%	Childhood traumatic events are reported as more common in IC/BPS pts than HCs

	and education	the ICPI, the MPQ-SF, the CES-D, the STAI, the FSFI, the MSPSS and the MOS SF-12	<i>vs</i> 14.7%; $P = 0.047$). Within the IC/BPS group, cases reporting previous sexual abuse endorsed > sensory pain, dep and poorer physical QoL at the present time compared to IC cases without a sexual abuse history	
Hepner <i>et al</i> [41], 2012	1019 females with BPS/IC symptoms	CS. In order to estimate SI prevalence in IC pts, females with and without recent SI were compared based on demographics, dep symptoms, BPS/IC symptoms, functioning, and treatment	11.0% (95%CI: 8.73-13.25) reported SI in the past 2 wk. Females who endorsed SI reported worse mental health functioning, physical health functioning, and BPS/IC symptoms. Multivariate logistic regression analyses indicated that BPS/IC symptom severity did not independently predict likelihood of endorsing SI	BPS/IC severity may not ↑ the likelihood of SI except <i>via</i> severity of dep symptoms
Keller <i>et al</i> [42], 2012	9269 pts (7584 females and 1685 male) with BPS/IC and 46345 (37920 females and 8425 male) randomly selected comparison ctrl	Lo. Case-control. Conditional logistic regression analyses were performed to calculate the odds ratio for each of the 32 medical comorbidities (included dep disorder, psychoses, alcohol abuse and drug abuse) between pts with and ctrl without BPS/IC	With the exception of metastatic cancer, pts with BPS/IC had a significantly ↑ prevalence of all the medical comorbidities analysed than ctrl without BPS/IC. Compared with ctrl without BPS/IC, pts with BPS/IC had particularly ↑ odds of comorbid mental illnesses	Pts with BPS/IC had > prevalence of multiple comorbidities
Clemens <i>et al</i> [43], 2012	3397 females with IC/BPS	CS. Pts completed a survey asking if they had comorbidities as IBS, FM, chronic fatigue syndrome, migraines, PA, or dep and the age of symptom onset. All pts were also asked to provide the date of IC/BPS symptom onset	2185/3397 females reported a diagnosis of at least one of the nonbladder conditions. Dep tended to occur earlier ($P < 0.05$), whereas FM generally occurred later ($P < 0.05$). Mean age of onset was lowest for migraine symptoms, dep symptoms, and PA symptoms, and greatest for FM and chronic fatigue syndrome symptoms. Mean age of irritable bowel syndrome and IC/BPS symptom onset was between these other conditions	These findings confirm the common co-occurrence of IC/BPS with chronic nonbladder conditions. In females with IC/BPS symptoms and coexistent nonbladder conditions, bladder symptoms do not uniformly predate the nonbladder symptoms
Katz <i>et al</i> [44], 2013	196 females IC (recruited from existing IC/BPS pts databases); mean age: 52 yr	CS. Examined mediation through structural equation modelling; MPQ, Pain Disability Index, CES-D; STAI; PCS	Negative affect ($P < 0.001$) and catastrophising ($P < 0.001$) significantly explained the relationship between impairments and functional disability, whereas social support did not	Negative affect and catastrophising partially explained disability in IC pts. Due to IC refractoriness, biopsychosocial patient management is essential. ↓ in negative affect and catastrophising will probably lead to improvements in pain-related disability. CS design does not allow for establishing causality
Keller <i>et al</i> [45], 2013	832 IC/BPS female pts and 4160 HCs (total = 4992) tracked for a 1-yr period; mean age 48.7 ± 16.2 yr	Lo. Cox proportional hazards regressions (stratified by age group and index year)	DD incidence = 4.69 (95%CI: 3.38-6.34) ×100 person-yr in pts with BPS/IC and 0.94 (95%CI: 0.68-1.27) ×100 person-yr in HCs. HR of DD during the 1-yr fup period for BPS/IC pts = 5.06 (95%CI: 3.21-7.96, $P < 0.001$). Adjusted HR for DD associated with BPS/IC = 10.33 for pts aged 40-49 (95%CI: 3.68-29.04)	↑ Risk for being diagnosed with DD during 1 st yr after receiving diagnosis of IC
Nickel <i>et al</i> [46], 2015	173 IC females	CS. case control. CES-D to assess dep, STAI for anxiety, PSS for perceived stress, PCS for catastrophising	157 pts (81%) reported more sensory type pain, poorer physical QoL, and greater somatic dep and sleep disturbance than 36 (19%) pts with pelvic pain only. This last phenotype reported ↑ IBS prevalence and fibromyalgia, and more general fatigue sym and psychiatric conditions	Two distinct pain location phenotypes, pelvic pain only and more than pelvic pain, were identified analysing IC/CPSP pts
Kairys <i>et al</i> [47], 2015	33 females with IC without comorbidities (mean age 39.5 ± 12 yr; mean symptom duration 9.1 ± 9 yr)	CS. Anatomical MRI data were acquired across 5 MAPP discovery sites; high resolution T1 structural images were acquired for each pt; Symptom were measure with the following questionnaires: SYM-Q; FGPI; PROMIS; sleep disturbance scale; SF-MPQ; HADS, Positive and Negative	Compared to HC(s), females with IC displayed significantly more GM volume in several regions including the right S1 ($P < 0.05$, FWE SVC), SPL/precuneus bilaterally (left $P < 0.05$, FWE SVC; right $P < 0.001$, uncorrected) and left SMA ($P < 0.001$, uncorrected, Table 1, Figure 1). GM volume in the right primary somatosensory cortex was	Alterations in somatosensory GM may have an important role in pain sensitivity as well as affective and sensory aspects of IC

		Affect Scale; Gracely Box Scales to measure pain and unpleasantness during the scan	associated with greater pain (McGill pain sensory total; $r = 0.396$, $P = 0.025$), anxiety (HADS, $r = 0.447$, $P = 0.01$) and urological symptoms ($r = 0.449$, $P = 0.01$)	
Chuang <i>et al</i> [48], 2015	16185 IC/BPS diagnosed during 2002-2010 [11865 (73.3%) females, 4320 (26.69%) male] <i>vs</i> 32370 HCs (23823 (73.60%) females, 8547 (26.40%) male); mean age 46 yr	Lo. Cohort study, based in part on data from NHIRD. Outcome risk assessed with Kaplan-Meier curves; Poisson regression analysis, and Cox proportional hazards models	IR (10000 person-yr) significantly ↑ in IC pts compared to HCs (92.9 <i>vs</i> 38.4 for anxiety; 101.0 <i>vs</i> 42.2 for depression, and 47.5 <i>vs</i> 23.0 for insomnia). IRRs of IC-associated anxiety and dep were ↑ in male compared to females (2.6 <i>vs</i> 2.4 for anxiety; 3.1 <i>vs</i> 2.3 for dep). IC remained a significant predictor with HR and 95% CIs 2.4 (2.2-2.7) for anxiety, 2.4 (2.2-2.6) for dep, and 2.1 (1.8-2.4) for insomnia	IC associated with ↑ risks of anxiety, dep, and insomnia in initially symptom-free pts
Griffith <i>et al</i> [49], 2016	424 pts with UCPPs [233 (55%) females, 191 (45%) males]; mean age 43.4 ± 15.1 yr	CS. MAPP Research Network. Scale GUPI, ICSI, ICPI. Aim of the study was also to examine relationships with symptoms of depression as a comorbidity of UCPPs	Dep was predicted by pain ($B \pm SE = 0.24 \pm 0.04$, 95%CI: 0.16–0.32, $P < 0.001$) In contrast dep was not significantly related to urinary symptoms (B , mean ± SE = 0.06 ± 0.04, 95%CI: 0.02-0.13, $P = 0.127$)	The data suggest that pain and dep are closely linked in pts with UCPPs, and that pain and urinary symptoms should be assessed separately
Tripp <i>et al</i> [50], 2016	(Tot 307 females pts) 190 IC mean age 49.20 ± 14.94 yr; 117 HCs mean age 47.83 ± 13.52 yr	CS. MPQ, IC syms, PHQ-9	23% IC pts endorsed SI in the past 2 wk <i>vs</i> 6% in HCs. In both IC pts and HCs, ↑ SI associated with ↑ pain and ↑ dep, whereas, for IC pts, ↑ SI was associated further with pain catastrophising	This study indicates that tertiary care pts with IC/BPS have an alarming rate of SI. Dep, catastrophising characterised by helplessness about managing pain, and pain are all significantly associated with ↑ SI. Catastrophising as a predictor of SI in IC/BPS points to its key role as a psychological predictor of negative pain-related outcomes
Kanter <i>et al</i> [51], 2017	15 females IC in a total of four focus groups. mean age = 52.6 yr, mean IC duration = 6.3 yr	Lo. Qualitative analysis of emerging themes. Session recording and transcription with information deidentified. Transcripts coded and analysed by three independent physicians	3 concepts identified: IC/PBS is debilitating, pts experience significant isolation, SI found in all groups	Pts with IC preferred organized treatment plans with diverse choices and providers who offered hope in dealing with their condition; focusing on the doctor-pt relationship to overcome isolation and suicidality, physicians may help IC pts
Abernethy <i>et al</i> [52], 2017	40 females (20 IC; 20 HCs); mean age 34 yr	CS study. Catastrophising Scale, PDI, BDI, BAI. Urinary microbiomes and cytokine levels analysed with standard immunoassay	Pts IC scored ↑ on dep ($P = 0.008$) and anxiety ($P = 0.019$) screens compared with HCs	IC pts' urinary microbiome less likely to contain <i>Lactobacillus</i> species and associated with ↑ levels of proinflammatory cytokines. No correlation between <i>Lactobacillus</i> species and cytokine levels
Chen <i>et al</i> [53], 2017	1612 IC pts, [1283 (79.6%) females, 309 male (20.4%) mean age 48.4 ± 16.4 yr] <i>vs</i> 3224 HCs (2466 females (76.5%), 758 male (23.5%) mean age 48.9 ± 16.4 yr). 1436 SoDi, 2872 non-SoDi. mean age 48.4 ± 16.4. IC pts 79.6% females HCs 76.5% females	Lo. Case-control and retrospective cohort studies. OdR for SoDi calculated with conditional logistic regression and HR for IC in SoDi pts estimated with Cox regression, cumulative risk with Kaplan-Meier	OdR for SoDi = 2.46. mean time until IC development in HCs = 11.5 ± 1.3 yr (shorter in SoDi pts, 6.3 ± 3.6 yr). HR for developing IC = 2.2. Pts and HCs differed in cumulative survival probability for IC ($P < 0.05$)	SoDi can be used as a predictor of IC. While examining pts with IC, it is recommended to investigate past history of SoDi
Chiu <i>et al</i> [54], 2017	94 females IC/BPS pts. mean age 40.6 ± 10.0 yr	CS. Link between urogenital syms, psychiatric syms, and potentially traumatizing experience CTQ, BVAQ, BDI-II, BAI, TDS	The high-CTQ group had ↑ dep, ↑ anxiety, ↑ dissociation, ↑ alexithymia and ↓ initial and follow-up bladder capacities. A combination of higher scores of cognitive alexithymia and lower scores of affective alexithymia was associated with ↑ bladder capacity	In pts with IC/BPS, ↑ anaesthetic bladder capacity was associated with a set of psychological factors that commonly prevail in functional somatic syndrome. This result suggests that a psychological mechanism independent of a bladder-centric defect may underlie the mental and somatic symptoms of a subgroup of pts with IC/BPS and that IC/BPS in a subgroup of pts may represent a functional somatic syndrome

Chiu <i>et al</i> [55], 2017	94 females IC/BPS pts. mean age 40.6 ± 10.0 yr. 47 females with AC. mean age 43.4 ± 9.9 yr	CS. Childhood trauma and urological sym in pts wit IC/BPS. FUP, OSQ, BBTS, BDI-II, TDS, BAI, SDQ-20	Pts in the IC/BPS group reported ↑ abusive experiences than did the AC group pts; however, this difference reached significance for physical abuse. Pts in the IC/BPS group reported ↑ childhood trauma by close others	The study hypothesizes that IC/BPS may be a heterogeneous condition that involves a multifactorial aetiology where a psychosocial phenotype of IC/BPS with a unique pathogenetic mechanism may exist; in which, CT may play an important role
Hosier <i>et al</i> [56], 2018	2007 pts (1523 male mean age 45 ± 13.5, 484 females mean age 45.7 ± 17.4 yr) with UCPPS from a single site	Lo. Retrospective study. Demographics. sym scores, pain scales, described clinical UPOINT scoring between 1998 and 2016 (data from UCPPS clinic)	Male had ↑ prevalence of dep (31% <i>vs</i> 18.4%), and ↑ alcohol use (44.2% <i>vs</i> 10.8%), ↑ IBS, ↑ chronic fatigue syndrome, ↑ fibromyalgia, ↑ drug allergies, ↑ diabetes compared to females with UCPPS (all $P < 0.001$)	Male with UCPPS have ↑ prevalence of systemic disorders/syms and worse urinary symptoms than females with UCPPS. Findings indicate that male and females with UCPPS have distinct and different clinical phenotypes
Liang <i>et al</i> [57], 2018	30 female pts IC undergoing several intravesical HA instillations with time <i>vs</i> 30 age-matched HCs	Lo. Prospective study. HADS, O'Leary-Sant score, PISQ-12, and a pain visual analogue scale completed before and after treatment; same for the HC	IC pts had a significant ↑ in HADS dep subscale and total scores. After HA treatment, 73% of IC pts showed ↓ in their urological syms, but no significant changes in HADS and PISQ-12 scores	Bladder pain and lower urinary tract syms in pts with IC/BPS may ↓ after a 6-mo intravesical HA treatment. No significant changes in psychological and sexual functional scores
Muere <i>et al</i> [58], 2018	341 females IC mean age 49.77 ± 14.49	CS. Demographics. CES-D, PCS. BCPCI	Pts who reported ↑ dep syms and with a ↑ tendency to catastrophize were more likely to engage in illness-focused coping strategies, which contributed to the reporting of ↑ sensory and affective pain	To manage pain in IC/BPS we need evidence-based techniques that ↓ catastrophizing, ↓ illness-focused coping, and ↓ dep. These techniques seem to function most in pts with ↑ dep
Van Moh <i>et al</i> [59], 2018	150 participants, 36% male (11/31) and 25% females (30/119) with HLs. The difference in median age was 17 yr (58 <i>vs</i> 41, $P < 0.001$)	Lo. Pelvic syms assessed with the following questionnaires: (1) ICSI, ICPI; and (2) PUF. Presence and distribution of non-urologic pain assessed with: (1) Self-reported history of IBS, fibromyalgia, chronic fatigue syndrome, migraine headache, vulvodynia (females only), and (2) using a body map diagram described previously to identify participants who reported "pelvic pain and beyond" and "widespread pain" patterns, and the number of pain sites beyond the pelvis. The intensity of non-urologic pain was assessed using a 0-10 numeric rating scale. BPI was used to assess pain severity and pain interference. Psychosocial health was assessed by: History of depression, history of anxiety attacks, and somatic symptom burden	27% ($n = 41$) had HLs (36% of male, 25% of females). Participants with HLs were significantly older (median age 58 <i>vs</i> 41, $P < 0.001$) and reported less intense urologic pain (5 <i>vs</i> 7, $P = 0.024$) but more nocturia (ICSI nocturia symptom score: 4 <i>vs</i> 3, $P = 0.007$). had less frequently a history of IBS (15% <i>vs</i> 36%, $P = 0.013$) and anxiety attacks (22% <i>vs</i> 44%, $P = 0.013$)	HLs can be identified in both females and male. The presence of HLs was associated with older age, less bladder pain, more nocturia, and lower probability of IBS and anxiety attacks
Rodríguez <i>et al</i> [60], 2019	233 females and 191 male UCPPS. Pts with sym duration < 2 <i>vs</i> ≥ 2 yr compared for sym severity, COPC, and mental health comorbidities	CS. HAD, PCS	Male (but not females) with UCPPS sym duration ≥ 2 yr had ↑ severe syms than those with < 2 yr ($P = 0.045$). Participants with shorter (< 2 yr) and longer (≥ 2 yr) sym duration were as likely to experience COPC	Sym duration did not appear to affect severity of UCPPS pain. male with UCPPS syms ≥ 2 yr experienced more severe urinary syms than male with syms < 2 yr
Carty <i>et al</i> [61], 2019	37 female pts with CUP+ 25 controls (mean age 45 yr, primarily Caucasian and relatively well educated, and more than half (58.9%) were married or in a committed relationship)	Lo. RCT. Females with CUP received either a single 90-minute life stress interview ($n = 37$) or no interview (treatment-as-usual control; $n = 25$). Self-report measures of pain severity (primary outcome), pain interference, pelvic floor symptoms, and psychological symptoms (anx and dep) were completed at BL and 6-wk fup	Pain severity was significantly ↓ at fup in the interview condition than the control condition ($F_{(1,58)} = 4.52$, $P = 0.038$), with a medium effect size. Within the interview condition, there was a ↓ in pain over time (ns), whereas among controls, there was ↑ in pain (ns). Pelvic floor symptoms were significantly ↓ at fup for the interview condition than the control condition ($F_{(1,58)} = 8.01$, $P = 0.006$), with a large effect size. The interview condition had a significant ↓ in pelvic floor symptoms over time ($t_{(36)} = 2.95$, $P = 0.006$), but controls	An intensive life stress emotional awareness expression interview improved physical but not psychological symptoms among females with CUP

			did not change ($t_{(24)} = 0.09$, $P = 0.93$). Finally, the two conditions did not differ at fup on pain interference ($F_{(1,58)} = 1.02$, $P = 0.62$), anx symptoms ($F_{(1,58)} = 0.30$, $P = 0.59$), or dep symptoms ($F_{(1,59)} = 0.20$, $P = 0.66$)	
Cepeda <i>et al</i> [62], 2019	3973695 eligible non-IC at BL from the general population (2011471 females, 1962224 male)	Lo. Comparative descriptive study using retrospectively recorded data in a US claims database (Optimum). The first outpatient visit was the ID for the general population, and the diagnosis of dep was the ID for pts with dep	3973695 people from the general population; 2293 (0.06%) developed IC within 2 yr [mean age (yr) 50.87 \pm 16.86 <i>vs</i> 47.47 \pm 18.30 of non-IC; $n = 1995$ (87%) females]. Of 249200 individuals with dep, 320 (0.13%) developed IC	\uparrow Incidence of IC in pts with dep. Pts who developed IC had \uparrow chronic pain conditions, dep, malaise, and inflammatory disorders
Thu <i>et al</i> [63], 2019	51 OAB [39 females, 12 males; mean age (yr) 53.8 \pm 11.9], 27 IC/BPS (all females; mean age (yr) 44.8 \pm 16.6), and 30 [17 females, 13 males; mean age (yr) 54.2 \pm 12.3] CTRL	Lo. Non-urolgic pain was assessed using a whole-body map and BPI. Urologic pain was assessed using the IC Symptom and Problem indexes, Genitourinary Pain Index, and 0-10 pain scale. Urogenital pain was assessed using a genital map, and report of pain related to bladder filling and urination	OAB pts with pelvic pain had worse urinary symptoms (OAB-q SS: 21.7 <i>vs</i> 17.2, $P = 0.025$; OAB-q HRQOL: 39.7 <i>vs</i> 25.4, $P = 0.015$; UDI-6: 16.5 <i>vs</i> 10.8, $P = 0.004$; IIQ-7: 16.2 <i>vs</i> 5.1, $P < 0.001$), anx (HADS-A, 10.1 <i>vs</i> 6.1, $P = 0.003$) and dep (HADS-D, 7.6 <i>vs</i> 4.1, $P = 0.004$) compared to OAB pts without pelvic pain. The P -value for PSS almost reached statistical significance ($P = 0.05$)	OAB pts has pain inside and/or outside the pelvis. The intensity and distribution of pain in OAB was intermediate between IC/BPS and controls. OAB pts with pelvic pain have worse urinary symptoms and PSS. Systemic processes such as central sensitization should be examined in this population
Lai <i>et al</i> [64], 2019	211 pts IC/BPS or chronic prostatitis/CPSP (159 females, 52 males; mean age [years] 43.1 \pm 15.9)	CS. Clinical variables included in k-means clustering (uro- and non-uro pain severity, urinary urgency, frequency and UPOINT scoring)	The k-means clustering algorithm identified 3 pt clusters: (1) Mild pelvic syms in approximately 30%; (2) severe pelvic syms approximately 40%; and (3) systemic syms approximately 30%. The clusters had an equal likelihood to have HLs in bladder	Pts in the systemic cluster were younger by approximately 5-7 yr and more likely to be females. They had the most severe urinary syms, the most severe pelvic and nonpelvic pain and were more likely to have chronic overlapping pain conditions, psychosocial issues (dep, anxiety and somatic syms) and poorer QoL than pts in the other two pelvic clusters
Crawford <i>et al</i> [65], 2019	135 females IC recruited from tertiary care clinics, mean age 52.57 yr	Lo. PHQ-9 for dep, PCS for pain, DERS for emotion regulation at BL, 6 mo, and 1 yr. Serial mediation was used to test models of pain, catastrophising, and dep	The significant indirect path was from BL dep to catastrophising at 6 mo to pain at 1 yr ($b = 0.10$; 95%CI: 0.0049-0.2520). Helplessness was the key factor of catastrophising driving this relationship ($b = 0.17$; CI: 0.0282-0.3826)	\downarrow Feelings of helplessness and \uparrow pt feelings of control are important ways to limit the effect of low mood on pt's pain experience. De-catastrophising interventions should be part of the referral strategy for IC sym management
Tu <i>et al</i> [66], 2020	212 females with moderate-to-severe dysmenorrhoea [166 with dysmenorrhoea (mean age 24.5 \pm 0.5 yr) and 46 dysmenorrhoea with bladder sensitivity (mean age 23.8 \pm 0.9 yr)], 44 HCs (mean age 23.8 \pm 1.0 yr), and 27 BPS pts (mean age 29.0 \pm 1.1 yr) aged 18-45 yr	Lo. Prospective cohort study. Medical/menstrual history and pain history were evaluated with questionnaires. Psychosocial profile and impact were measured with PROMIS and a BSI	Participants with dysmenorrhea plus bladder pain had PROMIS Physical T-scores of 47.7 \pm 0.9, lower than in females with dysmenorrhea only (52.3 \pm 0.5), and healthy controls 56.1 \pm 0.7 ($P < 0.001$). Similar specific impairments were observed on PROMIS for anxiety, depression, and sleep in participants with dysmenorrhea plus bladder pain <i>vs</i> healthy controls	Females with dysmenorrhea who are unaware they also have bladder sensitivity exhibit broad somatic sensitivity and elevated psychological distress
McKernan <i>et al</i> [67], 2020	27 females with IC/BPS (mean age = 45 \pm 16.30 yr)	CS. 27 females with IC/BPS participated in a focus group and completed validated self-report assessments evaluating urinary symptoms, pain emotional functioning and affective vulnerability using PHQ-9 and PROMIS	Pts voiced pervasive and severe emotional distress related to IC/BPS. They acknowledged the reciprocal nature between emotional states and symptomology, with emotional distress both preceding and following symptoms. Both anxiety and depression symptoms were correlated with overall severity of IC/BPS, $r_{PROMIS} = 0.48$, $P = 0.013$; $r_{PHQ-9} = 0.68$, $P < 0.001$	The physiological and emotional consequences of IC/BPS were reported, highlighting their impact on interpersonal relationships and challenges obtaining appropriate treatment for IC/BPS. Dep symptoms appeared to better capture the role of psychological factors better than anx symptoms since quantitative analysis showed dep levels were significantly associated with worsened IC/BPS symptomology
Krsmanovic[68], 2020	87 females IC/BPS, mean age = 46.3 \pm 14.6 (treatment group = 49; controls = 38)	Lo. Case-control study. 49 pts enrolled in the online self-management treatment program+38 controls. Outcome measures divided into primary	Study pts did not obtain statistically significant improvements in physical and mental QoL, dep, pain catastrophising, or social support following study completion	Given the lack of understanding of pathophysiological mechanisms of this condition, and the inadequacy of medical treatment, it is pertinent to develop treatments that can

		(physical and mental QoL → SF-12) and secondary outcomes (IC/BPS syms → ICSI/ICPI, pain → VAS, dep → PHQ-9, pain catastrophising → PCS, social support → MSPSS, disability → PDI). Primary outcome completed at BL, mid-study (week 5), endpoint (1-wk post survey/program completion), and during 3-mo fup assessment. Measures on IC/BPS syms and disability completed at BL and endpoint only, pain, dep, pain catastrophising, and social support assessed at all timepoints		improve pt outcomes
Volpe <i>et al</i> [69], 2020	2301 females with IC and 4459 females with CPP and OAB (mean age IC group = 53.1 ± 15.5 yr; mean age OAB/ CPP group = 52.5 ± 13.6 yr)	CS. Case-control study. Pts were enrolled using the ICD-9 or ICD-10 diagnosis code for IC/BPS. Using ICD-9 and ICD-10 codes they identified comorbidities common in IC/BPS population including history of dep, history of alcohol abuse, history of PTSD	At BL, females with OAB and CPP were more likely to identify as minority ($P < 0.001$). Anx (57.3% <i>vs</i> 49.5%), dep (39.0% <i>vs</i> 46.0%), and PTSD (29.7 <i>vs</i> 26.4%) were all more common in the CPP and OAB group than in the IC group	A history of depression ($P = 0.030$) and IBS ($P = 0.021$) were statistically more prevalent among females with IC/BPS than HC
Clemens <i>et al</i> [70], 2020	A total of 191 male and 233 females with IC/BPS or CPPS	Lo. Prospective cohort study Pts were followed for 12 mo with bimonthly completion of SF-12 to assess general mental and physical HRQOL and with biweekly assessment of condition-specific HRQOL using GPI	Higher levels of BL problems most connected to the domain seemed to be the best predictors of declining outcome on that domain after controlling for initial HRQOL levels. Mental HRQOL outcomes were impacted by being male, BL UCPPS sym(s), widespread pain, non-urologic medical sym(s), and all measured psychosocial variables. Stress, dep, and being male remained independently associated with poorer HRQOL, Dep Score OR 0.907 (0.840–0.980) $P = 0.0130$, Perceived Stress OR 0.932 (0.894–0.972) $P = 0.0010$, being male OR 0.580 (0.380–0.885) $P = 0.0115$	These findings primarily highlight the impact of psychosocial factors on the HRQOL of UCPPS pts. Clinicians who treat UCPPS should involve mental health care in the management of pts who exhibit syms of dep, stress, or poor coping
Lai <i>et al</i> [71], 2021	385 females and 193 males with UCPPS. Among them, 12.5% had HL and 87.5% did not	Lo. COPC were assessed using the CMSI. Anx and dep were assessed using HADS. Stress and pain catastrophising were assessed using PSS and CSQ respectively. Quality of life measures included the SF-12 and GUPI	UCPPS without HL also had higher anx (HADS 7.2 <i>vs</i> 4.1), perceived stress (PSS: 15.9 <i>vs</i> 12.5), and pain catastrophising (CSQ: 11.9 <i>vs</i> 8.3) than those with HL, but there was no difference in dep	UCPPS pts without HL were more likely to have a systemic pain syndrome outside the pelvis compared to those with HL associated with more psychosocial syms
Crawford <i>et al</i> [72], 2021	Females' pts with IC/BPS (T0) → n 226, mean age = 49.29 ± 15.67; (T2) → n 183, mean age = 51.53 ± 15.47; (T3) → n 151, mean age = 53.22 ± 14.82	Lo. Pts were asked to complete the same set of questionnaires at T0, 6 mo after the initial urology appointment (T2) and 1-yr post-appointment (T3). Those included: Demographics. SF-MPQ, PCS	SF-MPQ score (mean ± SD): T0 = 16.77 ± 11.19; T2 = 14.27 ± 11.32; T3 = 13.11 ± 10.98; PCS score (mean ± SD): T0 = 23.68 ± 14.39; T1 = 19.88 ± 14.36; T3 = 17.96 ± 3.05; early changes in magnification predicted later changes in pain ($P < 0.001$); early changes in pain predicted later changes in rumination ($P = 0.03$); early changes in pain predicted later changes in helplessness ($P = 0.03$); and early changes in helplessness predicted later changes in pain ($P = 0.001$)	Pain catastrophising should be considered a prime target in psychological treatment for chronic pain in pts with IC/BPS
Laden <i>et al</i> [73], 2021	872 IC/BPS pts; mean age = 57.1 ± 15.3 yr [355 (41%) male, 517 (59%) females] and 558 non-IC/BPS pts mean age = 53.9 ± 16.2 yr; [291 (52%) male, 267 (48%) females]	CS. Case-control study Pts were identified from random samples of females and male pts with and without an ICD-9/ICD-10 diagnosis of IC/BPS. Presence of comorbidities and psychosocial factors (alcohol abuse, PTSD, sexual trauma, and history of dep) were determined using ICD-9 and ICD-10 codes	The odds of psychosocial factors was higher in the IC/BPS cohort (OR = 1.9; 95%CI: 1.5–2.4; $P < 0.001$). Notably, the odds of a PTSD diagnosis were higher among IC/BPS pts than non-IC/BPS pts (OR = 2.0; 95%CI: 1.5–2.5; $P < 0.001$), like Dep History (OR = 2.0; 95%CI: 1.6–2.6; $P < 0.001$). Health behaviours including alcohol abuse, smoking history, and diabetes were not	This study bolsters the existing literature that psychosocial comorbidities are more common among IC/BPS pts and vary by sex

			significantly different between IC/BPS and non-IC/BPS pts ($P = 0.083$, $P = 0.067$, $P = 0.626$ respectively). females IC/BPS pts had greater odds of psychosocial factors than male IC/BPS pts (OR = 1.9; 95%CI: 1.3-2.8; $P < 0.001$). The females IC/BPS pts had a significantly higher prevalence of sexual trauma compared to the females non-IC/BPS pts (13% vs 6%, $P < 0.05$), while none of the male, IC/BPS reported sexual trauma	
Lee <i>et al</i> [74], 2021	Male = 1.479 (49.3%); females = 1.521 (50.7%); Age: 40 s = 1.037 (34.6%); 50 s = 982 (32.7%); 60 s = 608 (20.3%); 70 s = 373 (12.4%)	Lo. All participants were surveyed using PUF, Patient Symptom Scale and GDS. The primary outcome was the prevalence of BPS-like symptoms, defined as a total PUF score of ≥ 12	The prevalence of BPS-like symptoms was 16.4% (483 of 3000 participants). females (21.4%) had a significantly > prevalence of BPS-like symptoms than male (10.7%; $P < 0.01$). The prevalence by age was significantly > in the 70 s group than in the other age groups ($P < 0.01$), and \uparrow significantly with the \uparrow severity of dep on the GDS ($P < 0.01$)	BPS-like symptoms are widespread among the general population of South Korea and can negatively affect many people's QoL
Yang <i>et al</i> [75], 2021	1103 IC/BPS pts and 4412 non-IC/BPS pts (5515; 4495 females, 1020 male). 81.5% females and 18.5% male, in both IC/BPS group and HC. Age: 22.57% < 35 yr; 30.28% = 35-50 yr; 25.93% = 50-65 yr; 21.21% > 65 yr	CS. Case-control study. The study investigated in the association between SRDs and a subsequent association of IC/BPS using ICD-9 codes	For all SRDs, the significantly increased risks were obtained in 2 yr before IC/BPS diagnosis, and the higher OR was observed within 3 mo before the diagnosis of IC/BPS. dep (OR = 1.54, 95%CI: 1.24-1.91), sleep disorders (OR = 1.45, 95%CI: 1.19-1.78), within 2 yr had a significant risk of IC/BPS. OR for dep [2.04 (1.52 to 2.75)] and sleep disorder [1.59 (1.18 to 2.15)] is even higher when they appeared in the past 3 mo	The study demonstrates that the health care for SRDs within the previous 2 yr is associated with an \uparrow risk of subsequent IC/BPS also the study demonstrates that most SRDs are associated with an \uparrow risk of subsequent IC/BPS, especially when peptic ulcer, IBS, dep, sleep disorders, and allergic rhinitis appeared in the past 3 mo
Tripp <i>et al</i> [76], 2021	Females IC/BPS pts ($n = 813$; range 18-80 yr, mean = 46.60 ± 14.10)	CS. This research reports suicide risk prevalence and its biopsychosocial predictors for a community IC/BPS sample. Pts were assessed with the following scales: SHS, PHQ-9, PAS, SBQ-R	Using the adult general population SBQ-R cutoff created an at-risk group ($n = 310$, M 9.73, SD 2.65) and a not at-risk group ($n = 503$, M 3.96, SD 1.11), with 38.1% of the sample meeting the suicide risk threshold. In the suicide risk group he predictors of greater risk included a previously reported exposure to suicide (odds ratio OR 2.71, 95%CI: 1.84-4.01), and the greater presence of psychological factors, such as psychache (<i>i.e.</i> psychological pain) (OR 1.04, 95%CI: 1.02-1.07), greater hopelessness (OR 1.12, 95%CI: 1.06-1.17), and more perceptions that the participant was a burden to others (<i>i.e.</i> perceived burdensomeness; OR 1.07, 95%CI: 1.03-1.11). Pts were also classified for pain group and predictors such as exposure to suicide, psychache, hopelessness, and perceived burdensomeness predicted suicide risk in all groups	The results confirm that suicide risk is a significant concern within the IC/BPS population and work is needed to understand how to address the increased needs of the at-risk females. Suicide risk is more related to psychosocial factors than physical IC/BPS factors. In particular, hopelessness, psychache, perceived burdensomeness, and exposure to previous suicide are important predictor
Brünahl <i>et al</i> [77], 2021	36 pts included in the intervention group [mean age = 48.6 ± 14.8 ; $n = 19$ (52.8%) females; $n = 17$ (47.2%) males] and 24 in the CTRL group [mean age = 50.6 ± 14.5 ; $n = 14$ (58.3%) females; $n = 10$ (41.7%) males]	Lo. Pts were non-randomly allocated to the intervention group with two consecutive treatment modules (physiotherapy and CBT) with a duration of 9 wk each or to the control group (treatment as usual) + Psychometric assessments (BL and post-treatment): GAD-7, PCS, PDI, PHQ-9, PHQ-15, PSQ, SF-12 PCS; SF-12 MCS; SF-MPQ total, SF-MPQ Sen, SF-MPQ aff., NIH-CPSI total Pain subscale, Urinary subscale, QoL subscale	The intervention group reported significantly \downarrow symptom burden as measured by the PDI ($P = 0.02$, $d = -0.73$), and the PHQ-9 ($P = 0.04$, $d = -0.62$), but no significant changes in the SF-12 and others	The combination of physiotherapy and psychotherapy for pts with CPSPS seems to be feasible and potentially promising with regard to effect
van Knippenberg <i>et al</i> [78], 2022	77 pts (46 females, 31 male), 29 with OBS	CS. Retrospective observational cohort study. The	An association was found between pelvic pain and anx ($P = 0.032$) and	The study reveals a pre-post comparison before and after

	and 48 with UPS (mean age = 54 yr, range 27-78)	objective of the study is to investigate the effect of integrated outpatient care by a urologist and a psychiatrist on the symptomatology of pts with functional urological disorders. Pts were screened with HADS, OAB-questionnaire and ICSI	panic disorders ($P = 0.040$). OR were 0.22 (0.06–0.76) for anx disorders and 0.26 (0.08–0.87) for panic disorders. An even stronger association was found between these variables in the group of urological pain syndromes ($P = 0.001$ in both groups). For anx disorders the OR was 0.02 (0.00–0.18) and for panic disorders 0.03 (0.00–0.24). A psychological trauma in the past was associated with a dep disorder ($P = 0.044$), with an OR of 2.93 (1.01–8.50). Of the pts with a psychological trauma in the past, 62.3% had urological pain syndromes and 83.3% suffered from pelvic pain. After a multidisciplinary intervention the integrated approach led to the following results: o difference is noticed in both groups ($P = 0.219$) in the HADS-Anx score before and after the multidisciplinary treatment. However, a significant 2-point reduction in the HADS-dep score is found ($P = 0.001$). The GAF score ↑ to the category 71–80, which indicates no more than slight impairment in social, occupational, or school functioning	multidisciplinary treatment by urologist and psychiatrist. A significant ↓ in HADS-depression scores was observed, and the GAF shows an ↑ in functioning
Yu <i>et al</i> [79], 2022	60 pts with IC/BPS, 55 females, 5 males (mean age = 53.5 ± 12.6 yr)	Lo. Pts with IC/BPS were randomized to the bladder monotherapy (BT) or combined CBT (CBT) group. The primary endpoint was the self-reported outcome GRA. Secondary endpoints included IC symptoms, BAI, and depression inventory, and objective parameters were also compared. Psychological assessments including DS14 PSS-10 were also performed	Post-treatment anxiety according to BAI showed significant improvement at 8 and 12 wk. Between-group changes also showed significant differences in BAI and GRA at 12 wk. The study showed a significant effect on self-reported treatment outcomes [$F_{(2, 108)} = 7.161, P = 0.001$] and anx severity [$F_{(2, 108)} = 3.519, P = 0.033$] within the CBT group	This study reveals that multimodal treatment including CBT combined with suitable bladder treatment was more effective than bladder treatment alone. The CBT intervention significantly improved subjective treatment outcomes and severity of anx in pts with IC/BPS with moderate anxiety refractory to conventional therapy
Wuestenberghs <i>et al</i> [80], 2022	1453 pts with dyspeptic symptoms, of whom 61% with FD. BPS present in 16% of pts without FD, 22.2% of pts with only FD and 36.4% of pts with overlapping FD and IBS. (mean age = 47.4 ± 15.7 yr, sex ratio male/females, = 0.35); 187 females and 53 males with BPS	CS. Functional dyspepsia and IBS were diagnosed according to Rome III and IV criteria. Pts were assessed with GIOLI to assess QoL, HADS for anxiety and depression, PSQI for sleep quality, and ISI for insomnia	In PTS with BPS overlapping with FD, dyspeptic symptoms severity, anxiety, depression, and insomnia levels were ↑, while quality of life and sleep quality were ↓, ($P < 0.05$ for all). These results were even more pronounced in case of overlap with IBS. Factors independently associated with overlapping BPS in FD pts were altered QoL and overlap with IBS	BPS is present in 26.9% of FD pts and is associated with higher gastrointestinal sym(s), psychological distresses, sleep symptom burdens, and with reduced quality of life. The presence of overlap with BPS or IBS in FD is associated with younger age, increased female predominance, reduced QoL, ↑ symptoms severity, ↑, anx and dep levels
Sutherland <i>et al</i> [81], 2023	55 females with IC (mean age = 55.05 ± 14.97 yr)	CS. The study focuses on the hypothesis that greater use of compensatory coping behaviours would be significantly associated with greater psychological distress. Compensatory bladder behaviours assessed with the OABq-QoL, anxiety and depression with the PROMIS	The use of coping strategies related to greater symptoms of depression, but not anxiety. Depressive symptoms positively predicted use of compensatory coping, $t_{(52)} = 2.33, P = 0.024$; while anxiety was not significantly related to compensatory coping, $t_{(52)} = 1.310, P = 0.142$	↑ Use of compensatory coping behaviours related to ↑ dep syms, even after controlling for level of bladder impairment
Şahin <i>et al</i> [82], 2023	35 BPS pts, (mean age = 50.2 ± 13.32; 24 females and 11 males	Lo. Pts were administered the KHQ, BAI, BDI, OAB-V8, and VAS at each visit. The same questionnaires were completed and compared with pre-pandemic scores to examine the possible clinical aggregation of the pandemic period on BPS pts	Three (8.6%) of our pts had an asymptomatic COVID-19 infection, but no one had an active disease diagnosis. The mean OAB-V8, BAI, BDI, and VAS scores of the pts at their last visits before the pandemic period were 8.54 ± 4.33, 5.66 ± 7.77, 5.37 ± 5.92, and 4.54 ± 2.03, respectively. All scores of these questionnaires ↑ during the	BPS pts have been negatively affected by the emotional effects of the COVID-19 pandemic and their BPS symptoms exacerbated

			<p>pandemic period, but only the OAB-V8 and VAS scores ↑ statistically significantly ($P = 0.02$ and 0.02, respectively)</p>	
Cardaillac <i>et al</i> [83], 2023	<p>CPP females with a HSS (High Score of sensitisation) → $n = 29$; mean age = 37 ± 10; CPP females with a LSS (Low Score of sensitisation) → $n = 24$; mean age = 40 ± 10</p>	<p>Lo. females with CPP and a HSS ($> 5/10$; $n = 29$) vs LSS ($< 5/10$; $n = 24$) according to the Convergences PP criteria underwent a non-invasive bladder sensory test, a rectal barostat test, and a muscular and a vulvar sensory test+ poststimulation pain (minutes), QoL (MOS SF-12/SF-36) and psychological state, comprising anx (STAI), dep (BDI-SF), and catastrophising (PCS), were assessed</p>	<p>Pts mostly suffered from endometriosis (35.8%), IBS (35.8%), BPS (32.1%), and vestibulodynia (28.3%). BL characteristics were similar. CPP females with a high sensitization score had more painful diseases diagnosed (2.7 ± 1.3 vs 1.6 ± 0.8; $P = 0.002$) and suffered for longer (11 ± 8 vs 6 ± 5 yr; $P = 0.028$) than pts with a low score. The bladder maximum capacity was equivalent between pts, however, the pain felt at each cystometric threshold was ↑ in females with HSS. A longer period was needed for pts with HSS to obtain a VAS $< 3/10$ after bladder (4.52 ± 5.26 vs 1.27 ± 2.96 minutes; $P = 0.01$), rectum (3.75 ± 3.81 vs 1.19 ± 1.23 min; $P = 0.009$), and muscles (1.46 ± 1.69 vs 0.64 ± 0.40 min; $P = 0.002$) stimulation. The psychological state was equivalent between groups. No association was found between the sensory thresholds and the psychological state results. The physical component of the QoL score was ↓ in females with HSS ($P = 0.0005$), with no difference in the mental component</p>	<p>There are objective elements to assess for the presence of central sensitization, independently of psychological factors; high- vs low-sensitisation pts did not differ on catastrophising</p>
Panisch <i>et al</i> [84], 2023	<p>133 females, diagnosis of CPP, aged 18-65 yr (mean age = 60%)</p>	<p>CS. All pts completed a survey assessing symptoms of somatoform dissociation (SDQ-20), PTSD, pelvic pain severity, history of CPP-related surgeries, and mental and physical HRQOL</p>	<p>17% had SDQ-20 scores ≥ 35 (cutoff). 60% had experienced at least 1 traumatic event and 57% had PC-PTSD-5 scores ≥ 3 (cutoff). Bivariate correlations revealed significant relationships between somatoform dissociation and PTSD symptoms ($r = 0.30$, $P = 0.12$) and mental ($r = -0.49$, $P < 0.001$) and physical ($r = -0.47$, $P < 0.001$) HRQOL. Inverse relationships were also found between PTSD symptoms and mental ($r = -0.49$, $P < 0.001$) and physical ($r = -0.37$, $P < 0.001$) HRQOL. Mental HRQOL was also correlated with seeking counselling services ($r = -0.34$, $P < 0.001$) and physical HRQOL was associated with pelvic pain severity ($r = 0.50$, $P < 0.001$) HRQOL. Multiple regression analysis revealed that mental HRQOL was significantly related to symptoms of both somatoform dissociation and PTSD and that physical HRQOL was significantly associated with pelvic pain severity and symptoms of somatoform dissociation. A post-hoc correlation analysis showed that pts with CPP had high correlations between Mental and Physical QOL measures and sensory alterations, more localized pain and functional difficulties related to the genital region and greater generalized analgesia and numbness in relation to the body as a whole</p>	<p>An integrated approach in care protocols for females with IC or CPP that takes into account assessments of trauma exposure and symptoms of somatoform dissociation should be encouraged</p>
Porru <i>et al</i> [85], 2023	<p>69 female pts, mean age = 49.4; 42 with BPS/IC + 27 with chronic non neoplastic pain</p>	<p>CS. Administered questionnaires included PHQ-9; ICSI-ICPI, BPI (pain short questionnaire), psychological interview; other psychosocial variables</p>	<p>Mean PHQ-9 scores, 10.3 in pts with IC/BPS and 6.9 in CTRL. The main SD in group 0 had a CI: 8.4-12.19, with 95% of pts having a total value in this range. The CI in the second group was 4.7-9.12 (the difference was statistically significant, $P < 0.02$)</p>	<p>BPI and CI have an important psychological impact; psychosocial factors are involved in the evolution of the clinical picture</p>

¹Chronological order is maintained. ↑: Increase, augmentation, elevation, improvement; ↓: Decrease, decreased, lower, diminution, worsening; Anx: Anxiety; BAI: Beck Anxiety Inventory; BCPCL: Brief Chronic Pain Coping Inventory; BDI: Beck Depression Inventory; -II: 2nd version; BL: Baseline; BoNT/A: Botulinum A toxin; BPI: Brief Pain Inventory; BPS: Bladder pain syndrome; BSI: Brief Symptom Inventory for somatic sensitivity; CBT: Cognitive behavioural therapy; CES-D: Center for Epidemiologic Studies Depression Scale; CFS: Chronic fatigue syndrome; COPC: Chronic overlapping pain conditions; CP: Chronic prostatitis; CPP: Chronic pelvic pain; CPPS: Chronic pelvic pain syndrome; CS: Cross-sectional; CSQ: Current Symptoms Questionnaire; CSS: central sensitivity syndromes; CTES: Childhood Traumatic Events Scale; CTRL: Controls; CUP: Chronic Urogenital Pain; DAQ: Drossman Abuse Questionnaire; dep: Depression/depressive; DD: Depressive disorder; dep: DERS: The Difficulties in Emotion Regulation Scale; DS14: Weng's Taiwan Type-D scale; EFS: University of Washington Ejaculatory Function Scale; FD: Functional dyspepsia; FM: Fibromyalgia; FSFI: Female Sexual Functioning Inventory; FUP: Follow-up; GDS: Geriatric Depression Scale; GIQLI: Access the Gastrointestinal Quality of Life index; GQ: General Questionnaire; GRA: Global response assessment; GUPI: Genitourinary Pain Index; HA: Hyaluronic acid; HADS: Hospital Anxiety and Depression Scale; HAM-A/D: Hamilton Anxiety/Depression Rating Scales; HC(s): Healthy control(s); HL(s): Hunner lesion(s); HR: Hazard ratio; HRQOL: Health-Related Quality of Life; IBS: Irritable bowel syndrome; IC: Interstitial cystitis; ICES: Interstitial Cystitis Self-Efficacy Scale; ICPI: IC Problem Index; ICSI: IC symptom index; ID: Index date; Inj: Injection; IIEF-EF: International Index of Erectile Function-Erectile Function Domain; IPIP: International Personality Item Pool; IR: Incidence rate; IRR: Incidence rate ratio; KGDS: Korean Geriatric Depression Scale; KHQ: King's Health Questionnaire; Lo: Longitudinal design; MD: Major depression; MOS SF-12/SF-36: Medical Outcomes Study Short-Form 12/36; QoL: Quality of Life; MPQ: McGill Pain Questionnaire; SF: Short form; MSPSS: Multidimensional Scale of Perceived Social Support; Questionnaire; NHIRD: National Health Insurance Research Database; NIH-CPSI: Prostatitis Symptom Index of the National Institute of Health; ns: Not significant; OAB: Overactive Bladder; OAB-V8: Overactive Bladder Form V8; OBS: Overactive bladder syndrome; OdR(s): Odds ratio(s); PA: Panic attacks; PAS: Psychache Scale; PCS: Pain Catastrophising Scale; PDI: Pain Disability Index; PHQ-9 DM: Patient Health Questionnaire Depression Module; PHQ-9: Patient Health Questionnaire 9; PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire; PROMIS: Patient-Reported Outcomes Measurement Information System Anxiety Scale; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; -10: Chen's perceived stress scale; pt(s): Patient(s); PTSD: Post-traumatic stress disorder; PUF: Pelvic Pain and Urgency/Frequency; RCT: Randomised control trial; RIISQ: Rome II standardised questionnaire; RR: Relative risk; SBQ-R: Suicidal Behaviors Questionnaire-Revised; SEAR: Self Esteem and Relationship; SF-36: 36-item Medical Outcomes Study Short Form; SF-MPQ: The Short Form-McGill Pain Questionnaire; SHS: State Hopelessness Scale; SI: Suicidal ideation; SoDi: Somatoform disorder; SRDs: Stress-related diseases; SSS: Self-Stigmatization Scale; STAI: State-Trait Anxiety Inventory; STAI-Y1: State anxiety; STAI-Y2: Trait anxiety; sym(s): Symptom(s); T: Student's *T*-test; UCPPS: Urological chronic pelvic pain syndrome; UPOINT: Urinary: psychosocial: organ-specific: infection: neurogenic: and tenderness Urological Treatment Program for Chronic Prostatitis; UPS: Urological pain syndrome; VAS: Visual analogue scale.

extensive databases[29,35,36], thus enriching the potential of identifying IC/BPS cases appropriately. Details of the assessment scales used are provided in Table 1.

There were 157 psychological research foci in the 63 eligible studies, *i.e.* about 2.5 foci per study. These were depression (56 studies), anxiety (31 studies), quality-of-life (QoL, 15 studies), catastrophizing (14 studies), sleep quality (9 studies), alcohol use disorder-related (4 studies, 1 also drug use disorder), perceived stress (4 studies), post-traumatic stress disorder (PTSD, 3 studies), sexual trauma (2 studies), or childhood abuse (2 studies), panic disorder (3 studies), somatoform disorders (3 studies), suicide-related issues (3 studies, one each suicidal ideation, suicidal behaviour, and psychache), general mental health (2 studies), emotional regulation (2 studies), and one study each alexithymia, dissociation, neuroticism, and psychosis.

Of the 56 studies that focused on depression, 22 found definitely increased levels of depression [mostly assessed with the Hospital Anxiety and Depression Scale (HADS)[86]] in patients with IC/BPS, while 5 found associations/correlations between having depressive symptoms and severity of IC/BPS. Longitudinal studies addressing treatment of IC/BPS found either no change in existing depressive symptoms post-treatment[57] or a decrease of depression with treatment [78]. Seven of the studies that investigated anxiety symptoms found a definite increase of these symptoms in the IC/BPS population, while all studies investigating functioning or QoL found them to be both decreased and impaired in this patient population. Of note, all studies addressing catastrophizing but two[46,68], found either high levels to correlate with anxiety and negative affect (depression)[25,44,52] or increased levels in IC/BPS patients compared to control populations[50] and also a beneficial effect of targeted psychotherapies[58,65]. Studies assessing suicidality showed contrasting results. One identified suicidal thinking in all IC/BPS groups[51], another showed that suicidal thinking was prominent in an IC/BPS sample, involving more than 38% of patients (more than the SBQ-R, Suicidal Behaviors Questionnaire-Revised[87] cutoff) and was most often accompanied by perceived burdensomeness, hopelessness and psychache[76], and still another found suicidal ideation to be independent from IC/BPS symptoms or the IC/BPS condition *per se*, but to be possibly mediated by depression[41]. One study related suicidal ideation to catastrophising in an IC/BPS sample[50]. Similarly, traumatised patients, either with PTSD or sexual or physical abuse, were more prone to develop IC/BPS. Such patients, as expected were found to have emotional distress and/or dysregulation[23,24,37,65,67]. We may speculate that any psychological symptom one wishes to investigate in IC/BPS has a high likelihood to be found altered.

Of the 63 included studies, 36 were carried out on women only, while the other 27 included patients of both sexes. This is a serious bias, since IC/BPS is found in both sexes, although they are more prevalent in women with female-to-male ratios varying from 1.6 in the United States[88] to 4 in China (Taiwan)[89]. Furthermore, it was not possible to calculate the exact number of participants in the various eligible studies, because many of them reported on the same databases through the years with variously overlapping samples (and participating sites). However, adding the figures provided in the studies involving both sexes, we obtained a female-to-male ratio of 1.034 (with total populations of 2041347 and 1974723, respectively), which is not credible, biased toward the male sex and does not match most epidemiological data.

Table 2 Studies emerging from searching the ClinicalTrials.gov site on the November 7, 2023. Strategy used: Condition/disease: Interstitial cystitis; Other terms: Psychological symptoms; Intervention/treatment: blank (not required)

Study title	NCT number	Dates	Status	Conditions	Interventions	Sponsor	Responsible	Results	Study type	Ref.
Smartphone-based Self-care Education Program for Women with Interstitial Cystitis: Educational Remote IC Aide	NCT05260112	February 17, 2022 Last, April 1, 2023	Completed	Cystitis, Interstitial	Other: ERICA	University of Pennsylvania, Philadelphia, PA, United States	Edward Kim	Submitted March 31, 2023, quality control still not concluded	Interventional	None
Interstitial Cystitis: Monitoring of the Psychic State and Counseling Intervention in the COVID-19 Era	NCT05752344	February 28, 2023	Completed	Cystitis, Interstitial	Other: Counselling	Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	Marianna Mazza	Not submitted; study conducted from November 1, 2020 to November 1, 2022	Observational	None
Safety and Efficacy of Aloe Vera in the Management of the Symptoms of Interstitial Cystitis	NCT04734106	February 1, 2021 Last, January 24, 2024	Not yet recruiting	Interstitial Cystitis Chronic Interstitial Cystitis Bladder Pain Syndrome	Drug: Desert Harvest Aloe Vera Capsules Other: Placebo Capsules	Wake Forest University Health Sciences, Winston-Salem, N.C., United States	Wake Forest University Health Sciences	Not started	Interventional	None
Biopsychosocial and Conventional Approach in Bladder Pain Syndrome	NCT05155384	December 10, 2021 Last, January 3, 2022	Unknown status	Interstitial Cystitis/Bladder Pain Syndrome, Randomised Control Trial	Other: Pain Neuroscience Education; Relaxation exercises; Cognition target exercise; Pelvic floor stretching exercises; Transcutaneous electrical nerve stimulation	Hacettepe University, Ankara, Turkey	Ceren Gursen	Some results submitted; quality control still not concluded; completion estimated October 15, 2022; no notice since then	Interventional	None
Study of Biomarkers and the Relaxation Response Using Guided Imagery in Women With IC	NCT00420550	September 1, 2007, Last March 21, 2012	Completed	Interstitial Cystitis Pelvic Pain	Behavioural: Relaxation Response using Guided Imagery, Phase 2	William Beaumont Hospitals, Royal Oak, MI, United States	Kenneth Peters	No results posted	Interventional	None
Quality of Life Analysis in Bladder Pain Syndrome/Interstitial Cystitis	NCT05630742	November 18, 2022, Last November 30, 2022	Completed	Interstitial Cystitis, Bladder Pain Syndrome, Quality of Life	Other: chronic non-neoplastic pain	IRCCS Policlinico S. Matteo, Pavia, Italy	Daniele Porru	Results not posted	Observational	Porru <i>et al</i> [75]
Identifying Predictors of Treatment Success in Painful Bladder Syndrome	NCT01410461	August 4, 2011, Last August 5, 2011	Unknown status	Painful Bladder Syndrome	Device: quantitative sensory testing; Ultrasound testing	Rambam Health Care Campus, Haifa, Israel	Lior Lowenstein, Dalia Kesner	No results posted	Observational	None

Bladder Instillations Versus Onabotulinumtoxin A for Treatment of Interstitial Cystitis/Bladder Pain Syndrome	NCT04401176	May 19, 2020, Last October 12, 2023	Completed	Interstitial Cystitis Bladder Pain Syndrome	Drug: Heparin & Alkalinized Lidocaine Bladder Instillation; Onabotulinum Toxin A, Phase 2	Walter Reed National Military Medical Center, Bethesda, Maryland, United States	Eva Kwong Welch	No results posted	Interventional	None
Interstitial Cystitis: Elucidation of the Psychophysiology and Autonomic Characteristics (ICEPAC) Study	NCT01616992	June 8, 2012, Last February 4, 2015	Completed	Interstitial Cystitis/Painful Bladder Syndrome Myofascial Pelvic Pain	Drug: Bupivacaine	Case Western Reserve University, Cleveland, Ohio, United States	Thomas C Chelimsky, Medical College of Wisconsin; Jeffrey Janata, University Hosp. Cleveland	Results not posted	Observational	Williams <i>et al</i> [150]
Vestibulodynia: Understanding Pathophysiology and Determining Appropriate Treatments	NCT03844412	February 15, 2019, Last November 29, 2023	Recruiting	Vestibulodynia Temporomandibular Disorder Fibromyalgia Syndrome	Drug: 5% lidocaine/5 mg/ml 0.02% oestradiol compound cream; Nortriptyline; Placebo cream	Duke University, Durham, North Carolina, United States	Andrea Nackley – Duke, Andrea Rapkin – UCLA, Erin Carey-Elizabeth Geller – Duke	To be completed on December 1, 2024 (estimated)	Interventional	None
Translational Research in Pelvic Pain	NCT04001244	May 16, 2019, Last April 4, 2023	Completed	Endometriosis Bladder Pain Syndrome/Chronic Pain	Differentiate between two types of pelvic pain condition (endometriosis-associated pain and bladder pain syndrome)	University of Oxford, United Kingdom – IBMC Porto, Portugal – Boston Children's Hospital – Michigan State University – Bayer Gröenthal GmbH – Esteve – Queen Mary University of London – Aalborg University – Endometriosis.org – International Painful Bladder Foundation – Pelvic Pain Support Network – King's College London – Universität Heidelberg – University of Edinburgh – Universität Jena – Universität Münster	Katy Vincent – University of Oxford	No results posted	Observational	Dimitriou <i>et al</i> [149]
Life-Stress Interview for Women With Chronic Urogenital Pain Conditions	NCT02286115	November 5, 2014, Last December 14, 2016	Completed	Chronic Urogenital Pain	Behavioural: Life-Stress Interview	William Beaumont Hospitals, Royal Oak, MI, United States	Jennifer Carty, Mark A. Lumley – Wayne State University	No results posted	Interventional	Imamura <i>et al</i> [151]; mentioned in Carty <i>et al</i> [152] and Carty[153]
Improving Female Sexual Wellness	NCT04824820	March 29, 2021, Last April 5, 2023	Completed	Urinary Incontinence, Sexual Dysfunction, Pelvic Organ Prolapse, Pelvic Floor Disorders, Interstitial Cystitis, Female Sexual Dysfunction, Hypoactive Sexual Desire Disorder, Sexuality Orgasmic Disorder, Sexual Desire Disorder	Behavioural: Vibrator	Cedars-Sinai Medical Center, Los Angeles, CA, United States	Karyn Eilber, principal investigator; contact: Alexandra Dubinskaya	No results posted	Interventional	None

Safety and Clinical Outcomes Study: SVF Deployment for Orthopedic, Neurologic, Urologic, and Cardio-pulmonary Conditions	NCT01953523	September 2, 2013, Last September 25, 2018	Completed	Neurodegenerative Diseases Osteoarthritis, Erectile Dysfunction, Autoimmune Diseases, Cardiomyopathies, Emphysema	Procedure: Administration of autologous adipose derived SVF	Elliot Lander, Rancho Mirage, CA, United States	Mark H Berman	Completed January 1, 2017; No results posted	Interventional	Wyles <i>et al</i> [154] and Khera <i>et al</i> [155]
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Data from ClinicalTrials.gov and internet searches.

DISCUSSION

This review showed a high prevalence of IC/BPS in the human female population and a high prevalence of psychological and psychiatric symptoms. There was an imbalance between male and female patients in favour of the latter in the sample taken into consideration in the eligible studies mainly because many studies excluded males. This way it is impossible to generalise on the psychological underpinning of this condition, but we may draw conclusions that may mostly apply to affected women.

IC/BPS is a condition affecting both sexes, although diagnosis is still a problem, and sex-related cultural factors may contribute to underdiagnosis in the male sex[90]. It is estimated that IC/BPS occurs between 2%-18% of the general population[91], with a female-to-male ratio oscillating between 6.5 and 12[92]. Although it is reported that there is an increased incidence of this condition, this may only be an impression[93] and is mainly based on data from some parts of the world where increased interest in searching the term on the internet[92], it is possible that this does not reflect true changes in incidence, but rather changes in diagnostic criteria and awareness (or unawareness)[94-96]. Diagnostic criteria differ among the various countries, so the differences reported on the prevalence of IC/BPS may depend both on how the condition is diagnosed in a specific country and on cultural or ethnicity factors and on when the study was performed. For example, a first study in Finland conducted on 960,000 people identified 95 women and 8 men with IC/BPS in 1975, *i.e.* a prevalence of 18.1/100000 women of all ages, while for both sexes the prevalence was 10.6/100000[93]. The incidence in this sample was 1.2/100000 women each year[93]. Twenty years later in the Netherlands another study found a prevalence of 8-16/100000 women, thus approximating the figures in the first Finnish study[97]. Meanwhile, in the United States, there were two studies, using different assessment methods and criteria, which found very different prevalence rates; one found a prevalence of 30/100000 in 1987 using mailed surveys of board certified urologists[94], the other reported a prevalence of 510/100000 in 1989 based on participants' self-reports in 1989[98]. A second Finnish report presented data obtained through self-reports of contacted people in a representative sample and identified a prevalence rate of 450/100000[99], much higher than the preceding study, which was based on medical record examinations[93]. A third Finnish study[100] and an Austrian[101] one administered the O'Leary-Sant IC symptom index and IC problem index[102] in 2005-2007 to women; one found a clinically confirmed probable IC prevalence of 230/100000 and of possible/probable IC of 530/100000[100], while the other found an overall prevalence of 306/100000, which was higher in the middle-aged group (40-49 years of age, who had a prevalence of 464/100000)[101]. Another United States study carried out in 2005 was also based on patient surveys and diagnosed them according to two criteria: pelvic pain for at least 3 months plus urgency or frequency for at least 3 months or the preceding plus pain increasing with bladder filling and/or pain relieved by urination; the prevalence of IC/BPS according to the first criterion was 11.2% in women and 4.6% in men, and according to the second criterion 6.2% in women and 2.3% in men, respecting the "more than twice as many women affected than men" principle with both widened and restricted criteria[103]. A still further United States study conducted in 2007 identified a prevalence of $\geq 197/100000$ among women and $\geq 41/100000$ among men[104].

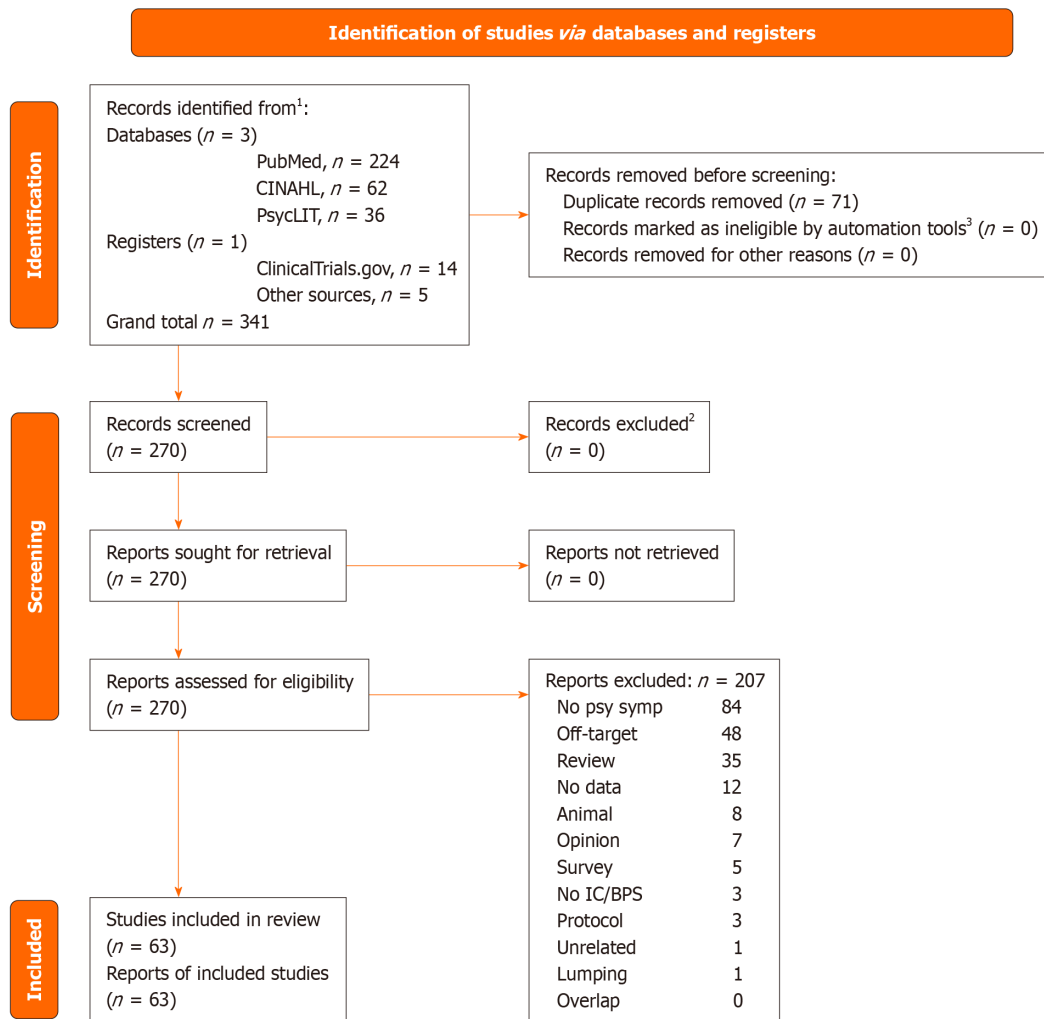


Figure 1 PRISMA flowchart of our search and inclusion procedures. ¹Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/register); ²If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools; ³No automation tools were used. IC/BPS: Interstitial cystitis/bladder pain syndrome.

Prevalence changes when using relaxed criteria and extend cases to people perceiving pelvic pain. A Boston (Massachusetts) study reported a point prevalence of 2% (1.3% in men and double as much in women) when defining painful bladder syndrome as “pain increasing as the bladder fills and/or pain relieved by urination for at least 3 months” [105]. Using high specificity and high-sensitivity definitions, 2.70% and 6.53% of American women met symptom criteria, respectively [106]. For men, high specificity definition applied to 1.9% of the sample and high sensitivity to 4.2% [107]. In the United States, prevalence of self-reported IC and clinician-rated IC symptoms were 3.7% and 4.4%, respectively, pointing to lack of overreporting of such symptoms among women; however, expanding to women reporting only pelvic pain, the prevalence rose to 17.3% [108]. Studies from Asian countries reported data similar to those of Western countries, *i.e.* 0.98% in the Fuzhu, Fujian province of China, based on mailed questionnaires [109], and 0.26% in South Korea in 2011, based on a telephone survey with the administration of the O’Leary-Sant IC symptom index and IC problem index [110], but a more recent study in South Korea, conducted 10 years later, based on an online survey and computer-assisted personal interviews and using structured questionnaires, reported an alarmingly high prevalence of 16.4%, with women (21.4%) being affected at a double rate than men (10.7%) [111]. The lack of uniformly adopted criteria and cultural changes may account for the discrepancies observed. It is curious that the annual incidence was always found to be low (or slow if you prefer), but from 1975 to 2008 it went from 1.2/100000 [93] to 15/100000 women [112]. How is it possible to have few cases each year and have also high total numbers of a condition? Something must be wrong with epidemiological calculations.

In special settings, as expected, higher proportions of cases meet criteria for IC/BPS. In a United States primary care setting, 13.1% patients scored high enough on the Pelvic Pain and urgency/frequency questionnaire [113] to suggest probable IC; again, women (17.5%) were approximately double than men (8.3%) [114]. In Spain, out of 9312 patients of both sexes attending functional urology and urodynamics units in the first 4 mo of 2014, 5.4% (*i.e.* $n = 503$) were diagnosed with IC/BPS, with 90% of them ($n = 453$) being women [115]. Despite the higher specificity of the Spanish services for capturing cases of IC/BPS, more cases were found in the rather aspecific United States setting. Cultural differences could account for this discrepancy. Furthermore, the male-to-female ratio was smaller in Spain. Summarising, both incidence and prevalence of IC/BPS appear to be rising, but rates are far from being established, since measuring

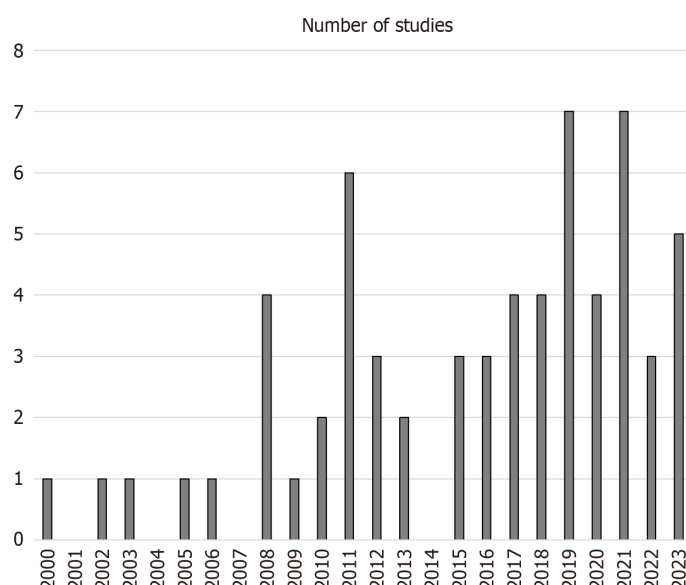


Figure 2 Per year distribution of eligible studies.

methods have not found consensus.

The question whether IC/BPS triggers psychological problems or it is triggered by already existing ones could be responded to by neuroimaging studies. Some few studies focused on the neuroimaging of IC/BPS. In December 2009, the “Multidisciplinary Approach to the Study of Chronic Pelvic Pain” (MAPP) Research Network was established and focused on various outcomes of female IC/BPS and its male counterpart, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)[116]. In 2012 there was a first animal model report[117], and by 2014, the first neuroimaging projects were set[118]. The MAPP network is based on collaboration between various North American university sites and encompasses various research focus areas, including epidemiology/phenotyping, neuroimaging/neurobiology, biomarkers, and urologic chronic pelvic pain syndrome (UCPPS) translational animal models[119,120]. The Network is still validating and fine-tuning its methods[121] and has already identified sources of inter-site variations among its recruiting sites in voxel-based morphometry (VBM), functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) measures despite using similar apparatuses for neuroimaging[122]. The MAPP Network and other studies have identified neuroimaging correlates of IC/BPS and CP/CPPS, collectively known now as UCPPS, which some are specific to UCPPS and others may extend to other chronic pain syndromes (Table 3)[47,123-140]. These involved both structural and functional neuroimaging, adopting 3 Tesla apparatuses and VBM, DTI, and proton magnetic resonance spectrometry (¹H-MRS) and functional connectivity based on fMRI. However, these studies identified only correlates through cross-sectional designs, and longitudinal follow-up studies within the Network did not focus on neuroimaging. There is need that the baseline and follow-up neuroimaging is performed and focused on changes accompanying the variations of the clinical status in order to establish causes and effects.

Another important issue linking chronic pain condition is the chronic pain patient’s tendency to catastrophise it. In our review we found evidence for the importance of pain catastrophising in the psychological symptoms displayed by IC/BPS-CP/CPPS patients[25,44,50,58,65,71,72]. Pain catastrophising, which is the patient’s bleak outlook about the outcome of his/her pain, is also present in other types of pain[141-144], and this has been shown to be related to emotional dysregulation[145]. We found the two constructs to be related also in women with IC/BPS[65]. It would be interesting to understand the neurobiological underpinnings of pain catastrophising and emotional dysregulation and whether altered brain functional connectivity matches the findings of functional connectivity alterations in UCPPS. For example, one hypothesis is that PC and pain perception is associated with reduced or higher neurotrophic factor levels [*i.e.* lower urinary brain-derived neurotrophic factor (BDNF) and higher nerve growth factor and vascular endothelial growth factor, which in turn would trigger neuroinflammation][16]. It is fascinating to investigate whether psychotherapy focusing on pain catastrophising or life stress, emotional awareness, and emotional expression can reduce perceived pain in IC/BPS patients through BDNF-related mechanisms. In fact, some psychotherapies have been reported to increase BDNF levels[146], which probably involves improvement in cognition, even in severely ill patients with psychosis[147]. Further steps would involve looking at which specific psychotherapy or pharmacotherapy obtains desired changes in the neurobiological signature of IC/BPS-CP/CPPS.

Another issue is the effect of integrated, interdisciplinary treatment of IC/BPS compared to single treatments, like pharmacotherapy, psychotherapy or physical therapies. In fact, it was recently shown that combining cognitive behavioural therapy with as-usual bladder treatment was superior to bladder treatment alone[148]. Unfortunately, there is only one such credible study available in the literature at this moment. Further replications of this study will pave the way to appropriate multimodal treatment in IC/BPS-CP/CPPS.

Table 3 Neuroimaging studies in urologic chronic pelvic pain syndrome, i.e. interstitial cystitis/bladder pain syndrome or chronic prostatitis/chronic pelvic pain syndrome and other pelvic or chronic pain conditions by year of publication

Ref.	Population	Technique	Findings
Farmer <i>et al</i> [123], 2011	Male 19 with CP/CPSP vs 16 HCs	fMRI during pain rating task; NMR, VBM; DTI	↑ FC in right anterior insula correlating with pain intensity; no GM differences between groups, but GM density in anterior insula and ACC correlated with pain intensity and chronicity; the normal correlation between WM FA and neocortex GM volume lost in CP/CPSP Pts
Bagarinao <i>et al</i> [124], 2014	Female 33 with IC/BPS (mean age = 39.51 ± 12.09 yr, 7 with vulvodynia and 8 with TMJD) vs 33 HCs (mean age = 38.95 ± 11.64 yr)	NMR, T1-weighted analysed with SPM8; used SVM algorithm; ROI approach	SVM predicted accurately to which group cases belonged in 73% of cases. SVM identified ↑ GM density areas in bilateral PSC, left preSMA, bilateral hippocampus, left amygdala. Correlation of ↑ cortical GM density with pain, symptom and mood self-ratings
Kilpatrick <i>et al</i> [125], 2014	Female 82 IC/BPS vs 85 HCs	fMRI, RS	Oscillation frequency power at lower frequencies ↑ in IC/BPS vs HCs in postcentral gyrus, anterior paracentral lobule, ventral and medial SMA and ↓ in right posterior insula; ↑ FC in Pts vs HCs between medial SMA and right midbrain, ventral SMA and cerebellum/bilateral midbrain, between anterior paracentral lobule and superior parietal Cx/cerebellum/right midbrain; ↓ FC in Pts vs HCs between right posterior insula and right medial insula
Farmer <i>et al</i> [126], 2015	Female 22 with IC/BPS (mean age = 37.73 ± 12.98 yr; no comorbidity or abnormal pelvis) vs 32 HCs (mean age = 32.84 ± 10.29 yr)	DTI, NMR T1-weighted, voxel-wise analysis	IC/BPS vs HCs ↓ WM density in left cerebellar corticospinal tract, right cerebellar ATR, right IFOF in right frontal orbital Cx, right ILF in lateral occipital Cx, left forceps major adjacent to precuneus, right ATR in right frontal pole, SLF in parietal Cx, and 8) temporal part of left SLF near ACC; ↑ FA in ILF, IFOF at right insula border, forceps major near left ACC, SLF in right postcentral gyrus and left PSC, and corticospinal tract passing through left PSC
Kutch <i>et al</i> [127], 2015	Male 28 with CP/CPSP vs 27 HCs	fMRI, RS	↓ FC between precentral gyrus/STG/IFG and right posterior insula in CP/CPSP Pts vs HCs
Gupta <i>et al</i> [128], 2015	Female 29 LPVD, 29 HCs, and 29 IBS	fMRI	Intrinsic connectivity LPVD > HCs in SMA, LPVD > IBS in left PMC, left and right SMA, IBS > LPVD in right STC and left and right PSC
Martucci <i>et al</i> [129], 2015	Female 45 UCPS vs 45 HCs	fMRI, RS	↓ FC in DMN in PoMeCx (left precuneus and PCC); ↑ FC between PCC and insula, DLPFC, thalamus, pallidum, putamen, amygdala and hippocampus; ↓ FC between left precuneus and OFC, ACC, VMPFC, AG, SPL, IPL
Kairys <i>et al</i> [47], 2015	Female 33 with IC/BPS (mean age = 39.5 ± 12 yr; no comorbidity) vs 33 HCs (mean age = 39 ± 11.6 yr)	VBM, NMR, T1-weighted analysed with SPM8 under MATLAB® 7.6	↑ GM volume in IC/BPS vs HCs; SVM identified ↑ GM density areas in bilateral PSC, left preSMA, bilateral hippocampus, left amygdala. Correlation of ↑ cortical GM density with pain, symptom and mood self-ratings
Woodworth <i>et al</i> [130], 2015	45 UCPS (19 female IC/BPS, 26 male CP/CPSP; mean age = 40 ± 14 yr) 56 HCs (26 female, 30 male, mean age = 38 ± 13 yr), 39 IBS (23 female, 16 male, mean age = 35 ± 12 yr)	DTI, 3T NMR post-bladder emptying; voxel-wise SPM; Pts were administered McGPQ and PANAS	↑ MD in UCPS vs HCs in left/right putamen, left globus pallidus, right posterior coronal radiate, right left forceps minor and GCC, SplCC, right/left sensorimotor integration fibres, right ACC, right external and internal capsules, left posterior SLF, right left ILF, left precentral gyrus association fibres, right prefrontal WM projections; ↑ MD in UCPS vs IBS in basal ganglia, right periventricular WM, temporal lobe projections, and fibres projecting to right primary motor cortex and association fibres in right hemisphere frontal areas; longer symptom duration correlated with MD and FA in WM clusters differing in MD between UCPS and HCs
Kleinhans <i>et al</i> [131], 2016	Female 10 twins (5 mono- and 5 dizygotic) discordant for UCPS (10 UCPS vs 10 asymptomatic)	fMRI, RS after urination and 50 minutes after drinking 1/2 Lt of water; 3T NMR. ROIs bilateral PAG and amygdala	The symptomatic twins reported more pain at all timepoints and more urgency before scan; ↑ FC in symptomatic twins following water consumption and stable thereafter; in asymptomatic twins, ↑ FC only after bladder distention; ↑ FC in in asymptomatic twins between right PAG and cerebellar/cortical regions involved in sensorimotor planning; ↑ FC between laterobasal amygdala to ACC, insula, somatosensory, premotor Cxs, thalamus and VMPFC

Wei <i>et al</i> [132], 2016	Female 46 PDM <i>vs</i> 49 HCs	fMRI during menstruation and periovulatory phase	PDM, adaptive hyperconnectivity between PAG and SMCx during painful menstruation; maladaptive hypoconnectivity between PAG and DLPFC and DMN during menstruation or periovulatory phase
Deutsch <i>et al</i> [133], 2016	Female 11 with IC/BPS (4 non-comorbid; 5 comorbid with fibromyalgia, 5 vulvodynia, 4 IBS, 3 chronic fatigue) <i>vs</i> 11 HCs	ASL fMRI rCBF at BL, empty bladder and heat pain; 3T NMR	At empty bladder, ↓ rCBF in bilateral insula, middle and PCC in Pts with IC/BPS <i>vs</i> HCs. Bladder distension associated with ↑ rCBF in IC/BPS <i>vs</i> HCs SMA, motor and sensory Cxs, bilateral insula, hippocampus, and middle and PCC in Pts with IC/BPS. During heat pain, ↓ rCBF in IC/BPS Pts <i>vs</i> HCs, who showed ↑ rCBF in bilateral amygdala
Huang <i>et al</i> [134], 2016	52 UCPPS (23 female, 29 male), 39 IBS (24 female, 15 male), 61 HCs (32 female, 29 male)	3T NMR, T1-weighted; DTI, FA	↑ FA in UCPPS in left corticospinal tract, left forceps major, left SLF at precentral gyrus; left superior corona radiata at ACC; forceps major, right IFOF, ILF and cingulum projecting to parahippocampal gyri at precuneus compared to IBS and HCs; ↑ FA in right ATR in IBS compared to HCs; regional changes independent of local grey matter FA and density
Kutch <i>et al</i> [135], 2017	52 UCPPS (34 female IC/BPS; 18 male CP/CPPS), mean age = 38.8 ± 11.9 yr	fMRI, RS; 3T NMR; clinical reassessment after 3, 6, and 12 mo	Strong BL FC, particularly in the fronto-parietal network, was associated with symptom improvement at 3 mo, but not at 6 mo or 12 mo. FC data predicted accurately the improver/non-improver status at 3 mo for 73.1% of the sample, with 69.2% sensitivity and 75.0% specificity; improver status was not maintained at later timepoints
Kutch <i>et al</i> [136], 2017	48 female (IC/BPS) 24 male (CP/CPPS) with UCPPS (n = 110) <i>vs</i> 23 female fibromyalgia <i>vs</i> 49 female HCs	fMRI, NMR	Pts with UCPPS and widespread pain show ↑ GM volume in right SMA and cingulate Cx and bilateral SMCx as well as ↑ FC between SMCx and insula with the salience circuit, compared to UCPPS Pts with localised pain and controls
Harper <i>et al</i> [137], 2018	Female 18 UCPPS (mean age = 34.8 ± 11.0 yr) <i>vs</i> 20 HCs (mean age = 34.7 ± 12.3 yr)	1H-MRS, T1-weighted scans; McGPQ, PANAS, HADS	UCPPS Pts had ↓ GABA and ↑ choline and choline-to-total creatine ratio than HCs in the ACC; the two groups did not differ for other metabolites (glutamate + glutamine; glutamate; N-acetylaspartate; and inositol); ↑ ACC choline level correlated with McGPQ pain, HADS Depression and PANAS negative affect scores
Woodworth <i>et al</i> [138], 2018	30 UCPPS (13 female IC/BPS; 17 male CP/CPPS); mean age = 39.9 ± 13.5 yr	DTI (FA, ADC), correlations with urinary proteins	ADC in a small WM cluster adjacent to right motor cortex correlated with urinary MMP2; ADC in a WM cluster in DRN and LCC correlated with MMP9 and MMP9/NGAL complex; FA in SMCx-connecting areas correlated with MMP9 as did midbrain areas and left SMCx with MMP9/NGAL complex; large WM clusters' ADC and FA correlated with NGAL urinary concentrations; no correlations with VEGF
Gupta <i>et al</i> [139], 2019	85 UCPPS mean age = 39.36 ± 12.80 yr (56 female IC/BPS, mean age = 38.96 ± 12.41 yr; 29 male CP/CPPS; mean age = 40.11 ± 13.71 yr) <i>vs</i> 86 HCs mean age = 37.90 ± 12.23 (59 female mean age = 35.44 ± 10.82 yr; 27 males; mean age = 49.60 ± 13.55 yr)	fMRI, RS; CTES to measure EALes. Network centrality was measured for each of the main brain networks* (DMN, basal ganglia, sensorimotor, executive control and salience) using graph theory	UCPPS Pts with → ↓ centrality in right anterior insula than HCs (salience network hub). UCPPS male → ↓ centrality in right anterior insula than male HCs. UCPPS female → ↑ centrality in right caudate nucleus and left angular gyrus than female HCs [condition effects]. UCPPS male → ↓ centrality in left PCC (DMN), angular gyrus, middle temporal gyrus, and superior temporal sulcus; UCPPS male → ↑ centrality in precuneus and anterior mid-cingulate Cx than UCPPS female [sex effect]. ↑ reports of EALes associated with ↑ centrality in left precuneus and left anterior mid-cingulate Cx in UCPPS female. Moderating effect of CTES on condition effect on betweenness centrality of right anterior insula (salience network hub); EALes moderated centrality in amygdala at high CTES scores
Fenske <i>et al</i> [140], 2020	100 UCPPS mean age = 39.2 ± 13.3 male/female = 34/66 <i>vs</i> 109 HCs mean age = 36.7 ± 12.2 male/female = 34/75	fMRI, RS; PAG characterisation as a ROI according to the MNI	↑ FC in HCs <i>vs</i> Pts in right (pars triangularis) and left IFG (pars opercularis); right PCC, left IFG (pars orbitalis) and left IPL shown when Pts and HCs were compared on the MNI-trace ROI compared to the MNI-sphere ROI

These studies probably used the same sample, but one reported some pain disorder comorbidity and the other no comorbidity. Sensorimotor Network: Superior Frontal Gyrus; Superior Frontal Sulcus; Precentral Gyrus; Precentral Sulcus; Postcentral Gyrus; Postcentral Sulcus; Supramarginal Gyrus; Posterior ramus (or segment) of the lateral sulcus (or fissure); Thalamus; Superior segment of the circular sulcus of the insula; Long insular gyrus and central sulcus of the insula. Basal-Ganglia Network: Nucleus Accumbens; Putamen; Caudate Nucleus; Pallidum/Globus Pallidus. Emotion Regulation Network: Pregenuar Anterior Cingulate; Subgenual Anterior Cingulate; Parahippocampal Gyrus; Hippocampus; Amygdala. Executive Control Network:

Inferior Frontal Sulcus; Triangular Part of the Inferior Frontal Gyrus; Superior Frontal Gyrus; Superior Parietal Lobule. Salience Network: Anterior Mid Cingulate Cortex; Anterior segment of the circular sulcus of the insula; Inferior segment of the circular sulcus of the insula. Default Mode Network: Marginal branch (or part) of the Cingulate Sulcus; Middle Temporal Gyrus; Superior Temporal Sulcus; Superior Temporal Gyrus Precuneus; Posterior Cingulate Cortex Angular Gyrus. H-MRS: Proton magnetic resonance spectroscopy; ACC: Anterior cingulate cortex; ADC: Apparent diffusion concentration; AG: Angular gyrus of the parietal cortex; ASL: Arterial spin labelling; ATR: Anterior thalamic radiation; BL: Baseline; CP/CPPS: Chronic Prostatitis/Chronic Pelvic Pain Syndrome; CTES: Childhood Traumatic Events Scale; Cx: Cortex; DMN: Default mode network; DLPFC: Dorsolateral prefrontal cortex; DRN: Dorsal raphe nucleus; DTI: Diffusion tensor imaging; EALEs: Early adverse life events; FA: Fractional anisotropy; FC: Functional connectivity; fMRI: Functional magnetic neuroimaging; GABA: γ -aminobutyric acid; GCC: Genu Corpus Callosum; GM: Grey matter; HADS: Hospital Anxiety and Depression Scale; HCs: Healthy controls; IBS: Irritable bowel syndrome; IC/BPS: Interstitial cystitis/bladder pain syndrome; IFG: Inferior frontal gyrus; IFOF: Inferior fronto-occipital fasciculus; ILF: Inferior longitudinal fasciculus; IPL: Inferior parietal lobule; LCC: Locus coeruleus and Barrington's nucleus complex; LPVD: Localized provoked vulvodynia; MD: Mean diffusivity; McGPQ: McGill Pain Questionnaire-Short form; MMP2: Matrix metalloproteinase-2; MMP9: Matrix metalloproteinase-2; MNI: Montréal Neurological Institute; NGAL: Neutrophil gelatinase-associated lipocalin; lipocalin-2; NMR: Nuclear magnetic resonance; OFC: Orbitofrontal cortex; PAG: Periaqueductal grey; PANAS: Positive and Negative Affect Schedule; PCC: Posterior cingulate cortex; PDM: Primary dysmenorrhea; PMC: Primary motor cortex; PoMeCx: Posterior medial cortex; Pts: Patients; PSC: Primary somatosensory cortex; rCBF: Regional cerebral blood flow; ROI: Region-of-interest; RS: Resting state; SLF: Superior longitudinal fasciculus; SMA: Supplementary motor area; SMCx: Sensorimotor cortex; SPL: Superior parietal lobule; SplCC: Splenium of the corpus callosum; SPM: Statistical Parametric Mapping; STC: Superior temporal cortex; STG: Superior temporal gyrus; SVM: Support vector machine; T: Tesla; TMJD: Temporomandibular joint dysfunction; UCPPS: Urologic chronic pelvic pain syndrome; VBM: Voxel-based morphometry; VEGF: Vascular endothelial growth factor; VMPFC: Ventromedial prefrontal cortex; WM: White matter; ↓: Decrease(d); ↑: Increase(d); →: Leads to: Show(ed).

CONCLUSION

An integrated clinical approach focusing on the patients' emotional and psychological state and global health and personalized treatments could ensure proper symptom control and promote adequate prevention of comorbidities and future disease-related implications[10]. Thus, it would be possible to cope innovatively with a complex and disabling condition, limiting the dramatic impact on patients' QoL, self-esteem, and social functioning. Future perspectives could involve finding neuroimaging alterations in people with IC/BPS that overlap with those of established alterations in psychiatric conditions which are frequently encountered in IC/BPS. However, to be sure whether alterations precede or follow the development of IC/BPS (the egg or the chicken dilemma), entire populations should be followed with neuroimaging data and look for the clinical evolution of selected people who subsequently develop UCPPSs. Although cross-sectional studies might tell us something about the factors determining IC/BPS, the 0.85 Longitudinal/cross-sectional ratio we found here should surpass the unit in future studies, should we understand the deeper underpinnings of IC/BPS-CP/CPPS. Future research should ascertain the reciprocal causal relationships between psychiatric/psychological factors and IC/BPS-CP/CPPS symptomatology in longitudinal studies, which are the only ones that could enable us to provide a response to the egg or the chicken dilemma. In fact, the simultaneous presence of factors does not legitimize us to establish cause and effect relationships, while factors present at baseline could be related or not related to a future development of a pathological trait.

ACKNOWLEDGEMENTS

The authors are grateful to the Scientific Administration of the Bibliographic and Bibliometric Support Service, Fondazione Policlinico A. Gemelli IRCCS, in particular, Dr. Maria Pattuglia, and Ms. Mimma Ariano, Ms. Ales Casciaro, Ms. Teresa Pioreschi, and Ms. Susanna Rospo, Librarians of the Sant'Andrea Hospital, Faculty of Medicine and Psychology, Sapienza University of Rome, for rendering precious bibliographical material accessible.

FOOTNOTES

Author contributions: Mazza M, Margoni S, Mandracchia G, Donofrio G, Fischetti A, Kotzalidis GD, Marano G, Simonetti A, Janiri D, Moccia L, Marcelli I, Sfratta G, De Berardis D, Ferrara O, Bernardi E, Restaino A, Lisci FM, D'Onofrio AM, Brisi C, Grisoni F, Calderoni C, Ciliberto M, Brugnami A, Rossi S, Spera MC, De Masi V, Marzo EM, Abate F, Boggio G, Anesini MB, Falsini C, Quintano A, Torresi A, Milintenda M, Bartolucci G, Biscosi M, Ruggiero S, Lo Giudice L, Mastroeni G, Benini E, Di Benedetto L, Caso R, Pesaresi F, Tracis F, Onori L, Chisari L, Monacelli L, Acanfora M, Gaetani E, Marturano M, Barbonetti S, Specogna E, Bardi F, De Chiara E, Stella S, Zanzarri A, Tavoletta F, Crupi A, Battisti G, Monti L, Camardese G, Chieffo D, Gasbarrini A, Scambia G, and Sani G conceived the review, designed it, discussed the details in Delphi rounds where consensus was reached, implemented searches, identified eligible articles, retrieved and analysed data in the articles, interpreted them, contributed substantially in drafting the paper, providing original ideas for further discussion, provided the final draft and agreed upon its final version; All authors read and approved the current version.

Conflict-of-interest statement: All authors declare having no conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers.

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S-Editor: Lin C

L-Editor: Filipodia

P-Editor: Zheng XM

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Bibliometric analysis of research in epilepsy and comorbid depression from 2014 to 2023

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Specialty type: Psychiatry

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Sarac E, Türkiye

Received: February 27, 2024

Revised: April 23, 2024

Accepted: April 28, 2024

Published online: June 19, 2024

Processing time: 111 Days and 0.5 Hours



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Abstract

BACKGROUND

Epilepsy and depression have complicated bidirectional relationships. Our study aimed to explore the field of epilepsy comorbid with depression in a bibliometric perspective from 2014-2023.

AIM

To improve our understanding of epilepsy and depression by evaluating the relationship between epilepsy and depression, bibliometric analyses were performed.

METHODS

Epilepsy and depression-related publications from the last decade were retrieved from the Web of Science Core Collection. We conducted bibliometric and visual analysis using VOSviewer and CiteSpace, examining authorships, countries, institutions, journals of publication, co-citations of references, connections between keywords, clusters of keywords, and keywords with citation bursts.

RESULTS

Over the past ten years, we collected 1045 research papers focusing on the field of epilepsy and comorbid depression. Publications on epilepsy and depression have shown a general upward trend over time, though with some fluctuations. The United States, with 287 articles, and the University of Melbourne, contributing 34 articles, were the top countries and institutions, respectively. In addition, in the field of epilepsy and depression, Professor Lee, who has published 30 articles, was the most contributing author. The hot topics pay attention to the quality of life in patients with epilepsy and depression.

CONCLUSION

We reported that quality of life and stigma in patients with epilepsy comorbid with depression are possible future hot topics and directions in the field of epilepsy and depression research.

Key Words: Epilepsy; Depression; Bibliometrics; VOSviewer; CiteSpace; Visualization analysis

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Core Tip: A total of 1045 publications explored the development of epilepsy and depression. Our study integrated bibliometric information to analyze the most influential authorships, countries, institutions, journals of publication, co-citations of references, connections between keywords, clusters of keywords, and keywords with citation bursts in the field of epilepsy and depression research. We then identified future hot topics and directions in the field of epilepsy and depression.

Citation: Chen L, He XH, Li XL, Yang J, Huang H. Bibliometric analysis of research in epilepsy and comorbid depression from 2014 to 2023. *World J Psychiatry* 2024; 14(6): 985-998

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/985.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.985>

INTRODUCTION

Epilepsy, a chronic neurological condition that impacts over 70 million individuals globally, is a group of brain neurons caused by transient abnormal discharge due to central nervous system dysfunction[1,2]. The World Health Organization ranks epilepsy as the second most burdensome neurologic disorder worldwide[3]. Epilepsy can affect both sexes and people of all ages worldwide, leading to social, behavioral, health, and economic consequences and significantly affecting the quality of life of patients[4,5].

Previous research indicates that epilepsy has an annual incidence rate of 0.614%, and compared with that in high-income countries, the incidence of epilepsy in low/middle-income countries is greater[5,6]. People with epilepsy experience a significant burden from comorbid conditions. The people with epilepsy, the prevalence of various illnesses such as depression, anxiety, dementia, migraine, heart disease, peptic ulcers, and arthritis is up to eight times higher compared to the general population[7-11]. A nationwide United States survey revealed that depressive disorders occur in approximately one-third of people with epilepsy[12,13].

Depressive disorder is a severe and common mood disorder and is one of the most widespread forms of psychiatric disorders worldwide[14,15]. In depressive disorder, hypothalamic-pituitary-adrenal axis abnormalities are well known. High instances of depression in epilepsy patients are likely linked to hormonal imbalances, which stem from the negative impacts of seizures and interictal epileptiform discharges on the hypothalamic-pituitary-adrenal axis[16]. In addition, the imbalance between GABA-mediated inhibition and excessive glutamatergic neurotransmission is involved in epileptogenesis[17], and disturbed GABA and glutaminergic neurotransmission has also been observed in individuals with depressive disorders[18,19]. Studies have shown that epileptogenesis can promote the production of excitatory amino acids, which leads to the activity of 5-hydroxytryptamine, and this is one of the main causes of depression[20]. A decrease in 5-hydroxytryptamine activity can also further induce epilepsy[21], indicating a bidirectional relationship between epilepsy and depressive disorder. An increasing number of studies have shown that depression in epilepsy patients has a specific biological basis[16,22-25]. Hence, summarizing the historical progression of research in the fields of epilepsy and depressive disorders is essential, and further exploring the mechanisms of epilepsy and depression comorbidity by bibliometric analysis and visualization provides a novel research focus and emerging topics.

Bibliometrics, first introduced in the early 1900s, formed an independent discipline in 1969[26]. This method involves analyzing published content along with its associated metadata as a quantitative approach to characterizing and assessing the evolution and advancement of a discipline or research field. It also includes visualizing the outcomes of the literature analysis through software that performs correlation analysis[27]. Bibliometrics has been widely used in the field of biomedicine because it provides a reliable basis for the diagnosis and treatment of various diseases and is reasonable[28]. Details such as authorships, countries, institutions, journals of publication, and co-citations of references can be obtained in the analysis process. Thus, the development of a field can be obtained through bibliometric analysis. To our knowledge, there has been no published bibliometric analysis focusing on epilepsy and depressive disorder. To fill this gap, we employed bibliometric tools VOSviewer and CiteSpace to determine the evolution and developmental frontiers of epilepsy and depressive disorder.

MATERIALS AND METHODS

Data collection and search strategy

Web of Science (WoS) is one of the most commonly used academic database sources[29]. For this study, data from the past decade were sourced from the WoS Core Collection (WoSCC) database. To minimize bias from daily updates to the database, literature collection from the WoSCC was conducted on a single day, that is, January 4 2024. We used TS = (("Epilepsy" OR "Seizure" OR "Convulsion" OR "Epileptic") AND ("Depression" OR "Depressive Symptoms" OR "Depressive Disorders")) AND WC = ("neurology" OR "Psychiatry" OR "neuropsychiatry"). The timeframe for the publications analyzed spanned from January 1, 2014, to December 31, 2023, and only original articles and reviews were included in the document types. In total, 2962 publications were incorporated into the study, with 2147 original articles and 440 reviews. Chen and He assessed the titles and abstracts, eliminating any research that was not unrelated to epilepsy and depression. The search strategy is depicted in Table 1 and Figure 1.

Analysis tools

In this research, bibliometric analysis and data visualization were performed using VOSviewer (version 1.6.20) and CiteSpace (version 6.2. R7). Initially, we exported the records obtained from the WoS into plain text files containing full records and references, labeled as download_XX.txt. Subsequently, these files were imported into VOSviewer and CiteSpace for conducting bibliometric and visual analysis. VOSviewer and CiteSpace are pivotal tools employed for bibliometric analysis and the identification of trends within scientific literature. VOSviewer and CiteSpace are adept at conducting comprehensive analyses across various dimensions, including countries, journals, authorships, co-citation journals, fronts, and emerging trends, by examining annual publication numbers, identifying growth trends, exploring the most commonly used keywords, and detecting keywords that have experienced significant spikes in citations over time.

RESULTS

Annual publications and prediction

This study utilized 1045 articles authored by 4647 individuals from 1587 institutions across 80 countries. These articles were published in 125 different journals and cited 26513 references from 5305 journals. A total of 1045 articles related to epilepsy and depression were published in a decade, which depicted an increasing trend and some fluctuations (Figure 2). Overall, over the past ten years, the number of published articles in the field of epilepsy and depression has remained steady at over 80 despite a few minor fluctuations, suggesting that academics are becoming increasingly interested in this area of research.

Analysis of the author

According to Pries' Law, the minimum number of articles written by a core author in a particular field $m = 0.749 \times n_{\max}^{1/2}$ (n_{\max} is the number of articles by the most productive authors in the field).

In our research, $m = 0.749 \times 30 \approx 4.10$. Therefore, authors with more than 4 articles (including 4 articles) are positioned as the core authors in this field. In the last 10 years, a total of 4647 authors contributed to the field of epilepsy and depression, and 182 authors published over 4 articles (Figure 3). Lee S emerged as the most prolific author in this field, who has published 30 articles. Their primary research focus is on comorbid mental health in people with epilepsy. Table 2 shows the highly productive authors who have published more than 15 articles in this field.

Analysis of journals

A total of 125 journals were included and visualized by using VOSviewer. As a result, between 2019 and 2021, the number of articles published in the majority of the journals was the greatest (Figure 4), which is consistent with Figure 1. Then, we summarized the journals with the top 10 most publications (Table 3) and found that the top 10 journals published 73.59% of the total publications ($n = 769$). Among the top 10 journals in epilepsy and depression research, *Epilepsy & Behavior* was the most active journal, with 481 publications, closely followed by *Epilepsia* with 80 publications, and the *Seizure-European Journal of Epilepsy* with 64 publications.

Analysis of countries and institutions

This study utilized 1045 articles authored by 4647 individuals from 1587 institutions across 80 countries. Firstly, the 30 countries with the most publications were visualized using VOSviewer and Microsoft Chartulator. The United States and England demonstrated the highest frequency of collaboration in this field, with Canada also showing significant cooperative involvement (Figure 5). Table 4 details the top five countries and institutions that are leading in publishing research on epilepsy and depression, providing a deeper analysis of those with high productivity. According to Table 4, we found that these five countries published 664 publications (63.54%), and the majority of publications were from the United States ($n = 287$, 27.46%), which received 5106 citations; however, England has the highest number of citations per paper, with 121 articles receiving 2786 citations, and each publication's average number of citations was 23.02. Moreover, publications from these top five institutions amounted to 145, accounting for 13.88% of the total, with the University of Melbourne leading with 34 publications, representing 3.25%, followed by the University of Ulsan ($n = 34$, 3.06%) and the University of Calgary ($n = 29$, 2.78%).

Table 1 Summary of the data sources and selection

Category	Specific standard requirement
Research database	Web of Science core collection
Citation indexes	SCI-Expanded
Searching period	January 2014 to December 2023
Language	English
Searching keywords	("Epilepsy" OR "Seizure" OR "Convulsion" OR "Epileptic") AND ("Depression" OR "Depressive Symptoms" OR "Depressive Disorders")
Document types	Articles and reviews
Data extraction	Export with full records and cite references in plain text format
Sample size	2962

Table 2 Top 5 most productive authors in the epilepsy and depression research field from 2014 to 2023

Rank	Author	Documents	Citations	Average citation/publication
1	Lee S	30	262	8.73
2	Sajatovic M	21	277	13.19
3	Jette N	18	698	38.78
3	Wiebe S	18	577	32.06
4	Kanner A	16	677	42.31
4	Patten S	16	553	34.56
5	Lin W	15	50	3.33

Table 3 The number of publications in the top 10 journals in the epilepsy and depression research field

Rank	Source	Publication	Citations	Average citation/publication
1	<i>Epilepsy and Behavior</i>	481	6740	14.01
2	<i>Epilepsia</i>	80	2221	27.76
3	<i>Seizure-European Journal of Epilepsy</i>	64	1178	18.41
4	<i>Epilepsy Research</i>	50	554	11.08
5	<i>Frontiers in Neurology</i>	28	331	11.82
6	<i>Acta Neurologica Scandinavica</i>	15	219	14.60
7	<i>Epilepsia Open</i>	14	47	3.36
8	<i>Frontiers in Psychiatry</i>	13	127	9.77
9	<i>Neurology</i>	12	233	19.42
10	<i>Epileptic Disorders</i>	12	88	7.33

Analysis of the most frequently used keywords

To identify the main areas of interest and emerging trends in epilepsy and depression research, we utilized VOSviewer to generate a map of keyword co-occurrences (Figure 6A). First, we analyzed the frequency of keyword occurrence in epilepsy and depression research. The brighter and wider the yellow range is, the greater the frequency of keyword occurrence. Table 5 lists the common keywords of the top 5 most common keywords: Depression (frequency: 643), epilepsy (frequency: 605), anxiety (frequency: 364), quality of life (frequency: 307), and people (frequency: 198). The five most prominent keywords prevalent in the current research literature underscore the focal areas of scholarly interest and investigation within the field.

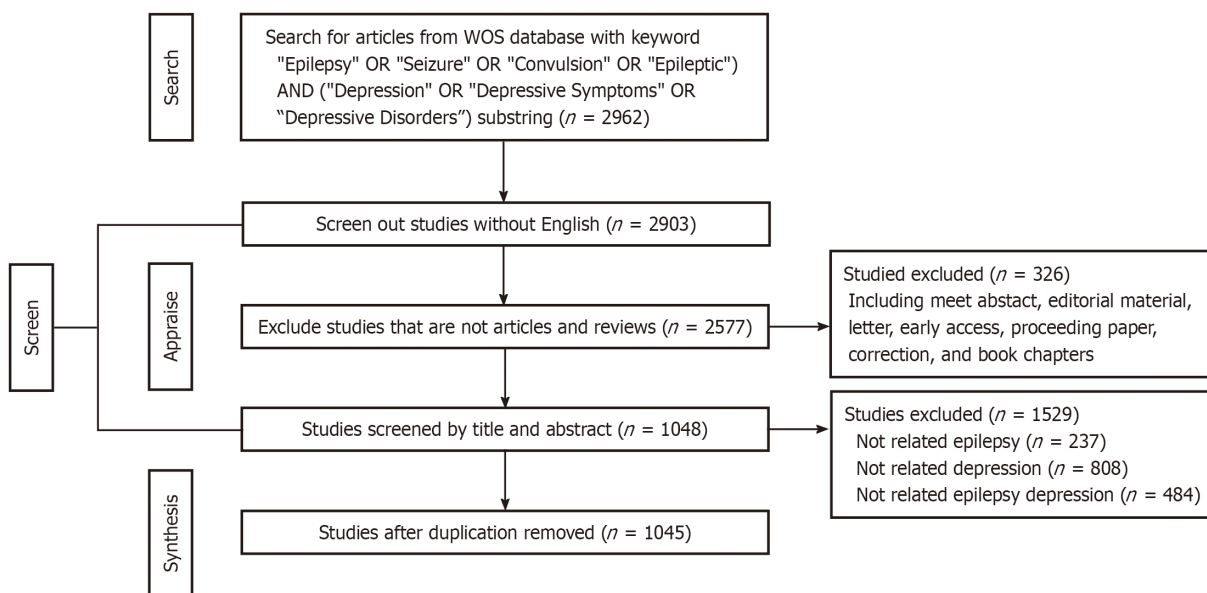
Then, we conducted a cluster analysis of co-occurring keywords using CiteSpace, resulting in the identification of eight clusters. The average silhouette (*S* value) of the cluster serves as a metric to assess the quality of clustering. Typically, an *S* value greater than 0.5 suggests reasonable clustering and an *S* value exceeding 0.7 indicates highly convincing clustering

Table 4 The top 5 countries and Institutions for publications in the field of epilepsy and depression research

Rank	Country	Publications	Citations	Institutions	Publications	Citations
1	United States	287	5106	University of Melbourne	34	411
2	England	121	2786	University of Ulsan	32	292
3	China	110	1205	University of Calgary	29	979
4	Canada	76	1717	Case Western Reserve University	28	358
5	Germany	70	1366	Kyungpook National University	22	523

Table 5 The co-occurrence keywords of the top 5

Rank	Keyword	Occurrences	Total link strength
1	Depression	643	5456
2	Epilepsy	605	5011
3	Anxiety	364	3235
4	Quality-of-life	307	2817
5	People	198	1834

**Figure 1 The selection of documents.**

[30]. All of the clusters achieved an *S* value over 0.5, indicating that the clustering results were reasonably reliable (Figure 6B, Table 6).

Analysis of co-citation references

A total of 26513 references were obtained from 5305 journals. First, we analyzed the five most important publications in epilepsy and depression research (Table 7). As we can see from Table 7, all five highly cited publications are articles. They are both dedicated to studying and assessing the quality of life of people with epilepsy. However, depressive disorders, which affect about one-third of patients with epilepsy, are the most prevalent psychiatric comorbidity and significantly decrease the quality of life in patients[12].

Figure 7 shows that the three most frequently cited journals were *Epilepsy Behavior* (7234 citations), *Epilepsia* (6133 citations), and *Neurology* (1757 citations) (Figure 7A). The journal co-citation consists of three clusters corresponding to the three colors in the figure (Figure 7B). The *Journal of Neurology* is excellent in JCR1, and the remaining two journals are excellent in JCR2. Among the three clusters, the journals in the green cluster are mainly related to epilepsy research, which is devoted to the most current information available on the behavioral aspects of seizures and epilepsy. The journals in the red cluster focus on psychiatric disorders, which involve the epidemiology, classification, and treatment of

Table 6 Analysis of the clusters of keywords in the epilepsy and depression research field

Cluster-ID	Silhouette	Mean	Included keyword (top 5)
0	0.651	2017	Temporal lobe epilepsy; depression-like behavior; mesial temporal lobe epilepsy; rij rat, and absence seizure
1	0.623	2017	High-risk people, Lebanese people, taking medication, family cohesion, and negative health events
2	0.610	2017	Family factor, psychogenic nonepileptic seizure, psychiatric disorder, emotional functioning, and patient caregiver
3	0.819	2016	Health-related quality, neurological disorders, depression inventory, risk factor, electroconvulsive therapy, and drug-resistant epilepsy
4	0.630	2017	Focal seizure, eslicarbazepine acetate, an antiepileptic drug, clinical practice finding, and Euro-Esli study
5	0.693	2016	Electroconvulsive therapy; magnetic seizure therapy; novel seizure quality index; ictal parameter; and case report
6	0.771	2016	Life depression, temporal lobe epilepsy surgery, prospective study, seizure freedom, and retrospective analysis
7	0.909	2018	Sleep quality, clinical features, sleep abnormalities, major determinants, and self-reported insomnia

Table 7 Top 5 most important publications in the epilepsy and depression research field

Rank	Title	Year	Citation
1	Quality of life of people with epilepsy: A European study	1997	182
2	Consensus statement: The evaluation and treatment of people with epilepsy and affective disorders	2008	171
3	Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy	2004	128
4	Epilepsy and risk of suicide: A population-based case-control study	2007	112
5	A brief questionnaire to screen for quality of life in epilepsy: The QOLIE-10	1996	111

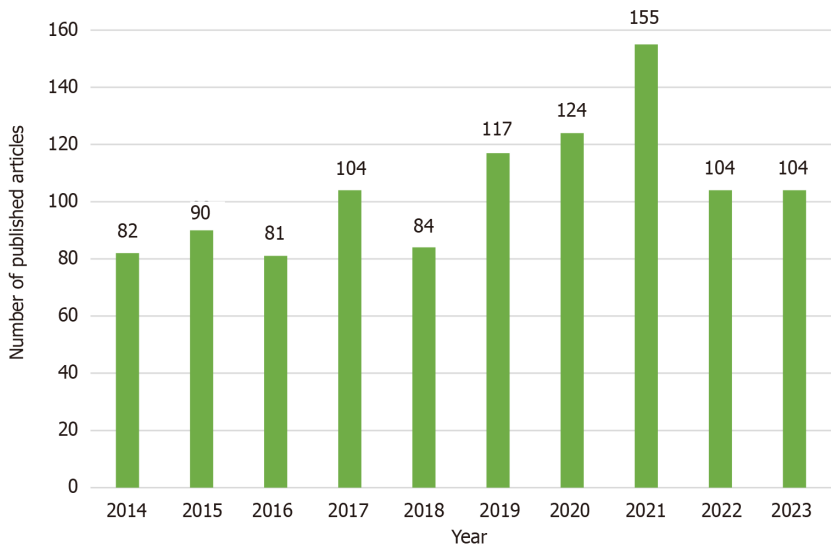


Figure 2 Distribution of publications from 2014 to 2023.

psychiatric disorders or the development and validity of measurement instruments. The journals in the blue cluster focus on the overall study of neurological diseases, which is devoted to the study of diseases and conditions of the nervous system.

Analysis of keywords with citation bursts

Finally, we created visualizations of the top 10 keywords that exhibited the most significant citation bursts between 2014 and 2023 (Figure 8). The blue line indicates the period, whereas the red line shows the period during which bursts of keyword citations occurred. The most intense explosive word is status epilepticus. The three most recent citation bursts occurred in 2022 (model) and 2022 (disorders depression inventory) and lasted until 2024 and 2021 (mental health); all of these bursts lasted until 2022.

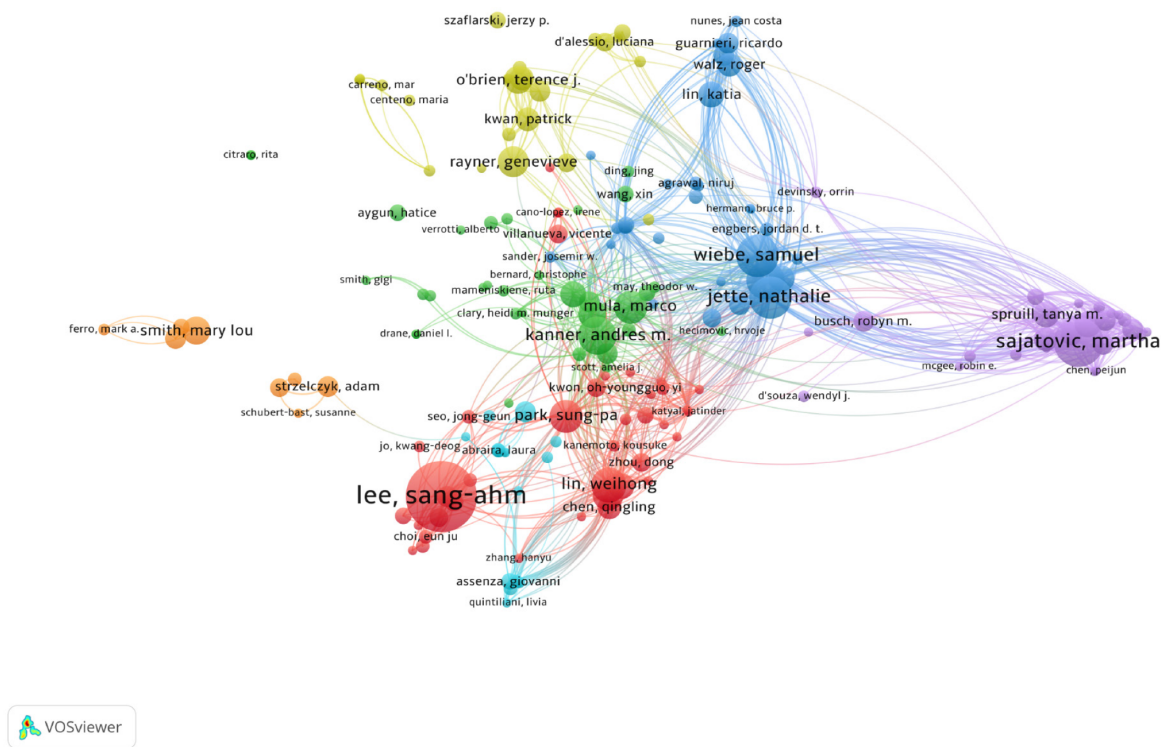


Figure 3 Network visualization of core authors. The larger the node is, the greater the number of published articles. The node connection lines represent the strength of the relationship between authors.

DISCUSSION

Status of epilepsy and depression research

Epilepsy and depression are known to have a bidirectional relationship[31]. Depression, notably the most frequent psychiatric comorbidity among epilepsy patients, greatly diminishes the quality of life[32]. Previous studies revealed that in patients with epilepsy, a nearly 2-fold increase in the risk of developing depression was observed[31]. Furthermore, if people are first diagnosed with depression, the risk of developing epilepsy increases 2.5-fold[33]. In addition, another study demonstrated that epilepsy is not only associated with an increased risk of depression but also with the severity of epilepsy[34]. Although the association between epilepsy and depression has been increasingly established and an increasing number of people have paid attention to the subject of epilepsy and depression in recent years, the dynamics and progress of the epilepsy and depression research field need further elucidation. Therefore, we used bibliometric analysis to study the link between epilepsy and depression.

Our study is the first to employ visualized bibliometric techniques to investigate the field of epilepsy and depression and revealed emerging topics and frontiers *via* VOSviewer and CiteSpace. Based on our findings, in the last 10 years, we identified 1045 articles authored by 4647 researchers from 1587 institutions across 80 countries, published in 125 different journals, and referencing 26513 citations from 5305 journals. The annual publication output showed steady growth in the research field. Especially from 2020 to 2021, researchers increasingly focused on epilepsy comorbid depression, leading to a record high in the annual number of publications on the topic. According to a previous report, compared to people without epilepsy, patients with epilepsy are more vulnerable to the psychological effects of the coronavirus disease 2019 (COVID-19) pandemic[35]. Thus, we speculated that the increase in publications is closely related to the COVID-19 pandemic. The COVID-19 pandemic has had far-ranging consequences for general physical and mental health[36]. To curb the spread of COVID-19, governments have undertaken measures such as forced house arrests, and mental and physical well-being have significantly decreased[37]. Although there has been no clear evidence thus far that COVID-19 can directly affect seizures, there is evidence that the COVID-19 pandemic has led to an increased risk of depression in epilepsy patients[38].

In our research, we recognized Lee S as the leading scholar in terms of productivity within the field of research on epilepsy and depression. Lee S from South Korea was devoted to studying related comorbid mental health in people with epilepsy, with topics such as anxiety, suicide risk, stigma with epilepsy, and perceived stress. However, Jette N, an author from the United States, had the highest average citation count per publication, who mainly focused on the analysis of epilepsy patients with complex comorbidities, and her articles were published in authoritative journals such as *Lancet*, *Nat Rev Dis Primers*, and *Neurology*. The average number of citations of Jette N was 38.78, which suggested that Jette N was the most influential scholar in epilepsy and depression research. In the author network, we revealed that only the authors who have a number of publications cooperate closely. The overwhelming majority of authors do not have cooperative relationships, which is not conducive to the development of epilepsy and depression research.

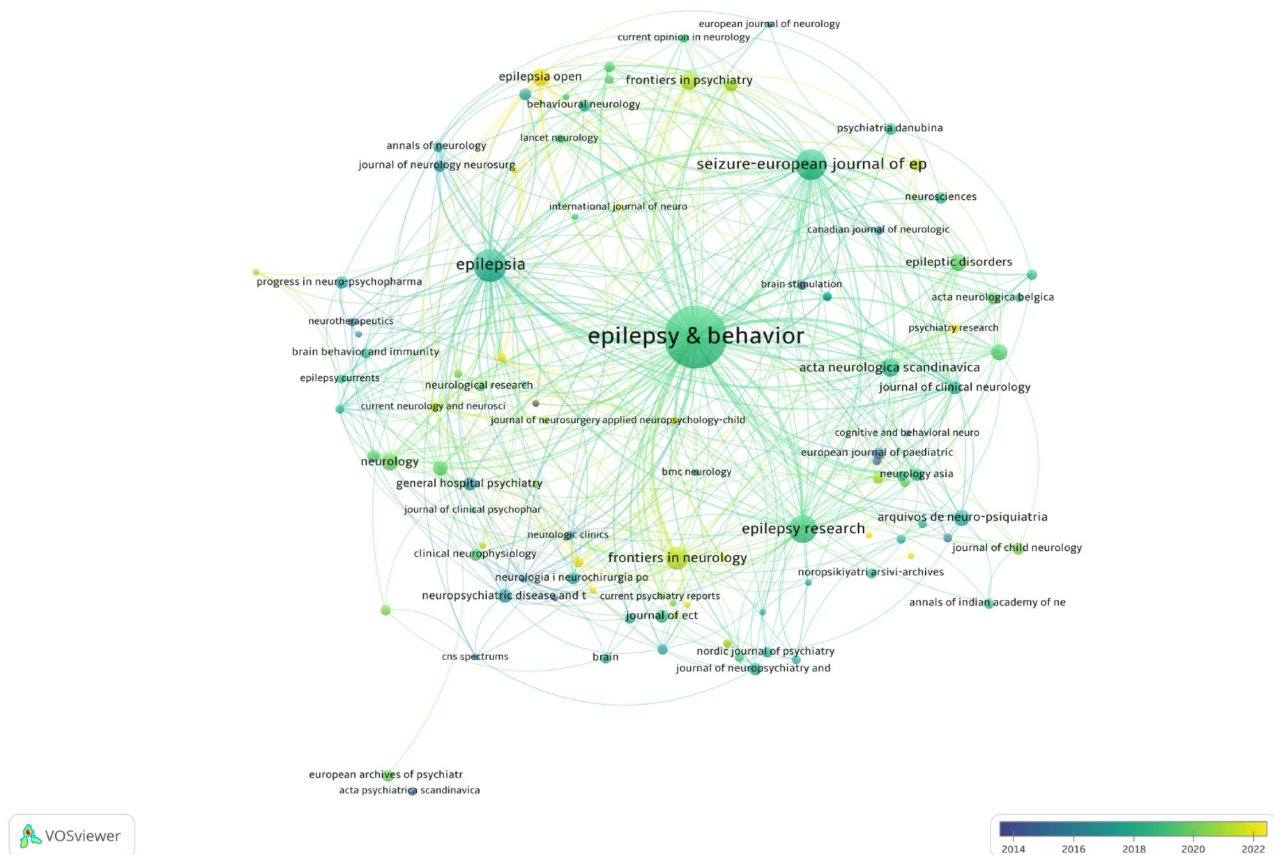


Figure 4 Visualization of the published journal network. The larger the node is, the greater the volume of published articles and the node connection lines represent the strength of the relationship between journals.

In our study, the bibliometric analysis summarized 125 journals from 2014 to 2023. *Epilepsy & Behavior* published the most papers on epilepsy and depression (46.0% of all articles), followed by *Epilepsia* (7.7% of all articles) and the *Seizure-European Journal of Epilepsy* (6.1% of all articles). The majority of the research originated from the United States (27.5% of all papers), followed by England (11.6% of all articles) and the People's Republic of China (10.5% of all articles). The United States held a dominant position in the field of epilepsy and depression research. The People's Republic of China is the only developing country in the top 5, and great achievements have been made in the epilepsy and depression research field in the past 10 years. Furthermore, among the five institutions producing the most publications, two were from Korea. It was closely related to Lee S, who was the most productive author who worked for the University of Ulsan. The nations and organizations that publish publications on this topic are not evenly distributed. As a result, more countries and institutions need to collaborate more on epilepsy and depression research for this field to advance.

Top 5 most cited papers related to epilepsy and depression research

Our findings highlight the five most cited publications on epilepsy and depression, consisting of 4 original articles and 1 review. In the 5 publications, 3 focused on the quality of life of patients. The article “Consensus statement: The evaluation and treatment of people with epilepsy and affective disorders”, published in *Epilepsy Behavior*, received the second most citations; this article presents a consensus statement dedicated to addressing depression across various age groups, including children, adolescents, and adults. This study proposes a detailed methodology for the diagnosis of affective disorders in individuals diagnosed with epilepsy, thereby contributing to a more nuanced understanding and management of psychiatric comorbidities in epileptic patients[39]. The purpose of citing these articles and journals is to analyze and review existing studies and to provide theoretical and empirical support for such studies.

Topics and leading edge in epilepsy and depression research

Keywords serve as a concise, high-level summary of an article's content. Frequently occurring keywords help pinpoint the central themes and emerging trends in a research field. Based on the keyword co-occurrence and cluster analysis by VOSviewer, the main current research trends include quality-of-life and high-risk factors in comorbid epilepsy with depression patients, depression in epilepsy patients caused by family factors, anxiety in patients with epilepsy and electroconvulsive therapy (ECT) for depression.

Quality of life is a broad-ranging and complex concept that affects a person's physical health, psychological state, social relationships, and relationships with salient features of their environment in a complex way[40]. Previous studies have shown that compared to healthy people, patients with epilepsy have less social support, lower rates of employment, and less social engagement[41-43]. These factors reduce quality of life. Siarava *et al*[44] reported that 1 in 4 patients with

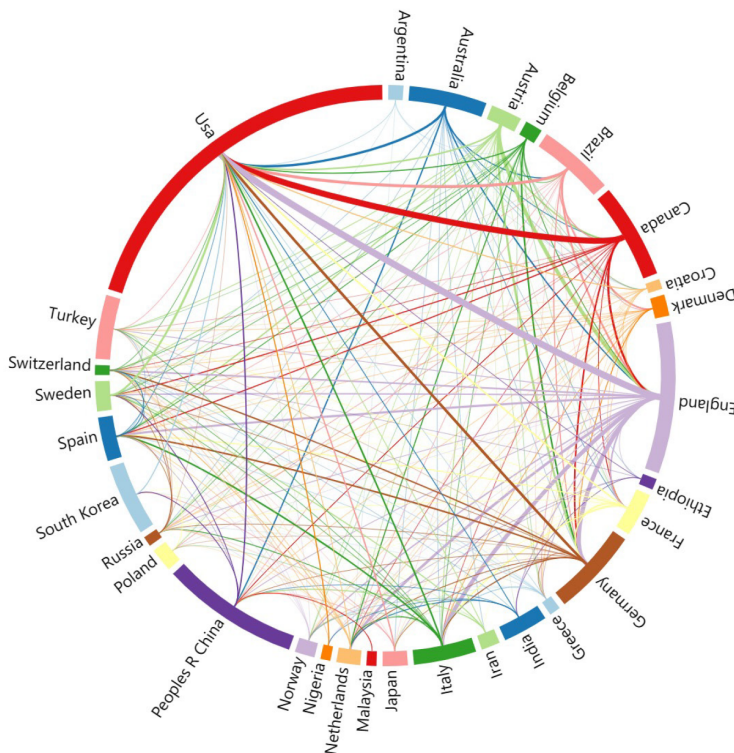


Figure 5 Cooperative relationships between countries. The thickness of the line represents the strength of the collaboration between countries.

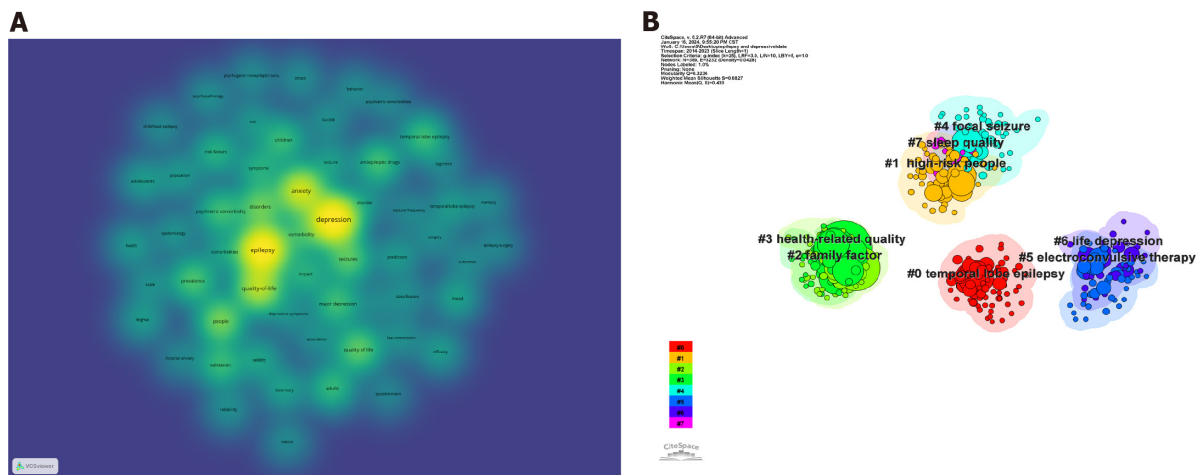


Figure 6 Analysis of the Keywords. A: The keyword co-occurrence map. The greater the density is, the greater the frequency of keywords that appear; B: Visualization of the keyword cluster analysis. Each cluster is depicted with a unique color.

epilepsy suffer from major depressive disorder. Studies have confirmed that higher rates of depression and anxiety are present in patients with epilepsy, which affects social cognition, further lowering the quality of life of patients[45,46].

Furthermore, compared to the general population, depression can even lead to suicidal ideation, which may be connected to depression[47,48]. Another important cause of depression in patients with epilepsy is adverse reactions to antiseizure drugs, such as barbiturates, phenytoin, and vigabatrin[49,50]. The presence of depression and the negative impacts of antiseizure drugs significantly affected the quality of life in patients[44].

Epilepsy often results in the loss of dignity. Consequently, patients with epilepsy might attribute their unemployment, absence of friendships, or relationship challenges to their condition. This attributional style has been associated with the development of depression[51]. While psychosocial factors are acknowledged contributors, the elevation in depression rates among individuals with epilepsy, as opposed to those suffering from other neurological and chronic medical conditions, may predominantly be attributed to underlying risk factors. These include genetic predispositions, as well as endocrine and metabolic anomalies, suggesting a complex interplay of biological mechanisms influencing the prevalence of depression in this population[50]. In addition, depression is the most commonly seen psychiatric comorbidity in patients diagnosed with temporal lobe epilepsy, particularly those exhibiting hippocampal sclerosis[52]. Co-occurrence of

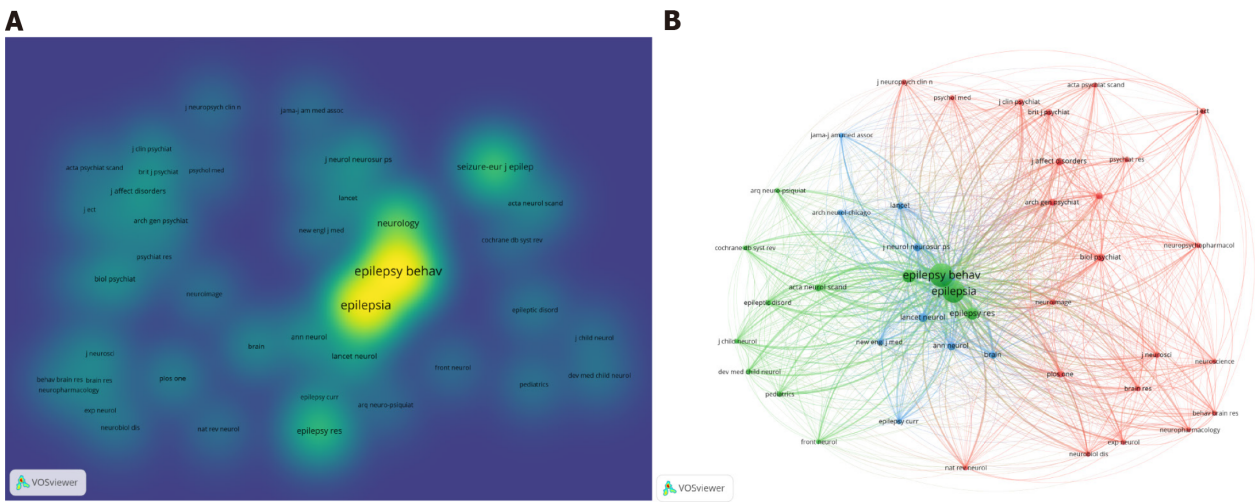


Figure 7 Co-citations of cited journals. A: The greater the density is, the greater the frequency of cited journals; B: The larger the node is, the greater the number of frequently cited journals. The node connection lines represent the strength of the relationships between keywords.

Keywords	Year	Strength	Begin	End	2014 - 2024
Suicidal ideation	2014	3.78	2014	2015	<div><div></div></div>
Seizure frequency	2014	3.28	2014	2016	<div><div></div></div>
Status epilepticus	2014	5.47	2015	2018	<div><div></div></div>
Multiple sclerosis	2015	3.42	2015	2018	<div><div></div></div>
Spanish version	2015	3.41	2015	2017	<div><div></div></div>
Ilae commission	2018	3.13	2019	2020	<div><div></div></div>
Frequency	2020	4.6	2020	2022	<div><div></div></div>
Mental health	2016	4.5	2021	2022	<div><div></div></div>
Disorders depression inventory	2022	3.53	2022	2024	<div><div></div></div>
Model	2017	3.22	2022	2024	<div><div></div></div>

Figure 8 The top 10 keywords with the strongest citation bursts.

temporal lobe epilepsy with hippocampal sclerosis and major depression is common in the clinic[53]. Visoná de Figueiredo *et al*[54] reported that 34.5% of patients with comorbid TEL and depression presented with hippocampal sclerosis as the structural substrate. Therefore, according to a meta-analysis by Cai *et al*[55], hippocampal sclerosis may be viewed as a significant risk factor for depression in patients with temporal lobe epilepsy.

ECT, a rapidly effective treatment for depression, has evolved over several decades[56]. ECT was employed as a treatment modality in patients with severe depression characterized by suicidal ideation or the presence of psychotic symptoms[57]. Several previous studies have shown that the quality of life of people with depression improved after ECT treatment, and this effect persisted for a long time[58]. Patients with depression who received ECT tended to have greater improvements in health-related quality of life than hospitalized patients with depression who received only antidepressants[59]. Moreover, Güney *et al*[60] reported that among patients with depression, male and female patients of all ages whose health-related quality of life significantly improved after treatment with ECT.

Moreover, they also found that compared with younger patients, elderly patients experienced greater improvements in mental health and social functioning after ECT, consistent with previous studies[60,61]. Although ECT is an effective treatment for depression, its disadvantage is that it is associated with side effects related to cognitive function, such as impaired learning and memory[62]. Therefore, patients should be informed of the risks and adverse effects associated with ECT, and patients must be thoroughly informed about the potential risks and adverse effects associated with ECT. Providing written information to both patients and their families is crucial, as it compensates for the possibility that patients might not retain verbal explanations over time.

CONCLUSION

Epilepsy and depression have a bidirectional relationship, and the two conditions often co-occur. To our knowledge, this is the first bibliometric analysis of epilepsy and depression research. This study conducted a bibliometric evaluation of the total scientific contributions in the fields from 2014 to 2023. We identified important publications, authors, journals, institutions, and countries and further analyzed the research network. Our study revealed that quality of life and stigma in patients with epilepsy comorbid with depression are possible future hot topics and directions in the field of epilepsy and depression research.

ACKNOWLEDGEMENTS

We thank Dr. Yi Zhou for his valuable academic advice.

FOOTNOTES

Author contributions: Chen L contributed to the drafting of the manuscript; He XH collected the data; Li XL conducted the analyses; Yang J interpreted the data and wrote the first draft; Huang H revised the article critically and guided the research process; and all the authors made significant contributions to the work reported, including the conception, design, planning of the study, interpretation of the results, and analysis of the data.

Supported by the National Natural Science Foundation of China, No. 81760247, No. 82171450, and No. 32160190; and The United Foundation of Zunyi City, No. Zunshikehe HZ Zi (2021)14.

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

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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