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MINIREVIEWS

Past, present, and future of deep transcranial magnetic stimulation: A review in psychiatric and neurological disorders

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Abstract

Deep transcranial magnetic stimulation (DTMS) is a new non-invasive neuromodulation technique based on repetitive transcranial magnetic stimulation technology. The new H-coil has significant advantages in the treatment and mechanism research of psychiatric and neurological disorders. This is due to its deep stimulation site and wide range of action. This paper reviews the clinical progress of DTMS in psychiatric and neurological disorders such as Parkinson's disease, Alzheimer's disease, post-stroke motor dysfunction, aphasia, and other neurological disorders, as well as anxiety, depression, and schizophrenia.

Key Words: Deep transcranial magnetic stimulation; Neurological disorders; Psychiatric disorders; Minireview

Core Tip: Deep transcranial magnetic stimulation as a novel non-invasive neuromodulation technique has been reported to be applied in clinical psychiatric and neurological disorders. The potential clinical efficacy and safety of this technique in each disorder and the mechanisms behind them need to be further summarized and sorted out, and the direction of future development needs to be more clearly defined.

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INTRODUCTION

Transcranial magnetic stimulation (TMS) is a magnetic stimulation technique that acts on the cerebral cortex, using electromagnetic principles to deliver an electric field to the cerebral cortex to alter the action potential of cortical nerve cells, thereby regulating metabolism and neural activity in the brain[1]. Repetitive transcranial magnetic stimulation (rTMS) is another form of TMS, which modulates cortical excitability. At high frequencies (> 5 Hz), cortical excitability increases, whereas at low frequencies (1 Hz), a long-term depression effect is produced and cortical excitability decreases [2]. TMS has been widely used to treat several neurological and psychiatric disorders, such as Parkinson's disease (PD), post-stroke limb movement disorders, and depression, with few adverse events. However, conventional TMS has some limitations[3,4], such as limited and imprecise localization of the stimulation site, which has led to the development of deep TMS (DTMS).

DTMS has the advantages of deeper and wider stimulation, more precise localization, and less damage to the superficial cortex than conventional TMS[5,6]. The depth of stimulation can be controlled by adjusting the intensity of the stimulation or the distance between the skull and the coil element. In recent years, this technique has been used to study and treat a variety of neuropsychiatric and psychiatric disorders and has been approved by the Food and Drug Administration (FDA) for the treatment of refractory depression. There has been an increase in national and international research on the use of DTMS in neurological and psychiatric disorders, but there has not been a systematic review of DTMS in the treatment of neurological and psychiatric disorders to evaluate its specific efficacy. This article presents a comprehensive review of the current state of research on DTMS in neurological disorders, such as PD and AD, and psychiatric disorders, such as schizophrenia (SZ) and depression, to provide a reference for future studies.

DTMS IN PSYCHIATRIC DISORDERS

Treatment-resistant depressive

Major depressive disorder (MDD) is one of the most common and disabling psychiatric disorders, with a prevalence of 5%-15% in the general population[7]. Approximately 30% of patients with MDD who do not respond to two or more trials of first-line antidepressants are considered to have treatment-resistant depression (TRD)[8]. TRD is a debilitating chronic mental illness that is associated with increased morbidity and mortality, reduced quality of life, impaired occupational, social, and offspring development, and increased costs on the healthcare system[9]. Currently, depression is mainly treated with medication, but antidepressants tend to be slow-acting and some of the active ingredients in depressants, such as neuropeptides, can be affected by the blood-brain barrier and cause some adverse effects[10].

Studies have shown that an active state of the left dorsolateral prefrontal cortex (PFC) is associated with depressed mood, and improvement of activity levels in the PFC may reduce depressive symptoms. Although TMS is effective in treating depression after stimulation of the dorsolateral PFC[11], there are limitations to this technique, such as the inability to produce some effect in areas such as deeper cortical and limbic areas, where deeper stimulation may be useful. DTMS is an effective new therapy and the FAD has approved the use of DTMS with H1 coils for the treatment of major depression[12]. So far, great results have been achieved with DTMS in the treatment of TRD. The development of DTMS applied to TRD is shown in Table 1.

Levkovitz *et al*[13] conducted a study to examine the impact of high frequency (20 Hz) repeat DTMS on the PFC in 65 patients with non-medicated depression. The researchers discovered that the use of high stimulus intensity resulted in significant improvements in both Hamilton depression rating scale (HDRS) scores and cognitive performance. Notably, no serious adverse events related to the treatment were observed. This study represents a pioneering exploration of the potential of DTMS in addressing psychiatric and neurological disorders[14]. Levkovitz *et al*[15] conducted a pioneering double-blind controlled randomized multicentre study aimed at validating the safety and efficacy of DTMS for the treatment of MDD. The study enrolled a total of 212 outpatients with MDD who had previously experienced treatment failure with antidepressants. The findings revealed a significant improvement in the HDRS-21 score, with a mean increase of 6.39 points in the DTMS group compared to only 3.28 points in the sham control group. Furthermore, the group that underwent DTMS stimulation demonstrated significantly higher rates of response and remission in comparison to the group that received sham stimulation. Moreover, the therapeutic impact of DTMS persisted throughout the 16-wk maintenance phase, proving to be advantageous for patients who had previously shown no response to alternative treatments[15]. The study findings revealed a remission rate of 60% [95% confidence interval (95%CI): 48%-71%] in the DTMS group, whereas the remission rate for rTMS with conventional figure-of-eight coils was 43% (95%CI: 31%-55%) (Table 1)[16-22]. In a meta-analysis conducted in 2019, it was observed that the DTMS group exhibited a response rate of 47.8%, whereas the sham group demonstrated a response rate of 25.6%. Additionally, the remission rate in the DTMS group was found to be 36.6%, while the sham group exhibited a remission rate of 14.8%. The criteria for response were defined as a 50% or greater improvement from baseline, as determined by the primary depression scale used in the study.

Table 1 Development of deep transcranial magnetic stimulation in treatment-resistant depression

Ref.	Method	Result	Adverse events	Significance
Levkovitz *et al*[13], 2009	20 Hz DTMS stimulates FPC	Significant improvement in HDRS scores	Headaches	This is the first time that TRD has been treated with the new H-coil
McGirr *et al* [14], 2014	20 Hz stimulates DLFPC	Reduction in HAMD-21 scores	Unreported	Five-factor personality assessment may have prognostic value in DTMS for resistant MDD
Levkovitz *et al*[15], 2015	20 Hz DTMS stimulates PFC	HDRS-21 score was improved by 6.39 points	Unreported	It is efficacious and safe in patients not responding to antidepressant medications, and the effect remains stable
Feffer *et al* [16], 2017	18 HZ DTMS stimulation; right abductor pollicis brevis muscle	Depressive symptoms (HDRS-21 total score) decreased significantly	Headaches	The severity of the depressive episode is associated with a positive therapeutic effect of dTMS
Kaster *et al* [17], 2018	18 HZ DTMS stimulates DLPFC and VLPFC	Remission rate was significantly higher with active than sham rTMS (40.0% *vs* 14.8%)	Pain and discomfort from stimulus	High-dose DTMS appears to be safe, well tolerated, and efficacious in the treatment of LLD
Tendler *et al* [18], 2018	10 HZ DTMS combined with SSRIs	The remission rate was 35.3%	Headaches	DTMS can augment formerly ineffective SSRI treatment
Filipčić *et al* [19], 2019	18 HZ DTMS stimulates LDLPFC	The response was significantly better in H1-coil than in 8-coil group (OR = 2.33; 95%CI: 1.04-5.21; P = 0.040)	Unreported	DTMS had better response rate than rTMS
Matsuda *et al* [20], 2020	18 Hz DTMS stimulates LDLPFC	HDRS-21 was more significantly improved	Unreported	DTMS might be effective and safe for office workers with treatment-resistant depression
Bahun *et al* [21], 2022	18 Hz stimulates DLFPC	Cognitive function all showed mild to moderate improvement	Unreported	Can improve MDD symptoms

DLFPC: Dorsolateral prefrontal cortex; HDRS-21: Hamilton Depression Rating Scale-21; DTMS: Deep transcranial magnetic stimulation; HAMD-21: 21-item Hamilton Depression Rating Scale; VLPFC: Ventrolateral prefrontal cortex; MDD: Major depressive disorder.

Remission, on the other hand, was defined as a HDRS-17 score of 7 or less, or a HDRS-24 score of 10 or less. Based on these findings, it can be concluded that DTMS is a safe and effective intervention for patients suffering from TRD. Studies combining DTMS and antidepressant medications seemed to show greater therapeutic effects[23].

From the above studies, it is clear that DTMS is an effective treatment for MDD and is well tolerated by patients without major adverse events, and may be a good option for patients who are antidepressant-resistant or ineffective.

Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a common and disabling psychiatric disorder characterised by the presence of intrusive thoughts and repetitive behaviors[24], with a lifetime prevalence of 2% to 23%[25]. It is characterised by early onset, which places a heavy burden on patients and their families. Currently, only 40% to 60% of patients can improve certain symptoms with treatment[26]. Studies have shown that the cortico-striatal-thalamic-cortical circuit is dysfunctional in patients with OCD[27], including the orbitofrontal cortex, anterior cingulate cortex (ACC), cingulate cortex, and ventral striatum[28]. A meta-analysis published in 2023 suggested that the average treatment response rate (percentage reduction in total Y-BOCS score) across studies was 39.5% for rTMS and 8.8% for sham conditions. rTMS showed a moderate therapeutic effect (g = 0.65) on OCD symptom severity and a threefold increased likelihood of treatment response (relative risk = 3.15) compared with sham conditions. Greater improvements in comorbid depression severity were associated with greater treatment effects of rTMS on OCD symptom severity. In addition, longer rTMS sessions and fewer total sessions predicted greater clinical improvement[29].

The development of DTMS applied to OCD is shown in Table 2. DTMS was first applied in 2015, when Modirrousta *et al*[30] found that 1-Hz frequency DTMS applied to Brodmann areas 24 and 32 improved OCD symptoms and Yale-Brown-Obsessive-Compulsive Scale (Y-BOCS) scores. In 2018, Carmi *et al*[27] noted a significant increase in Y-BOCS scores with high-frequency (20 Hz) deep magnetic stimulation and the ability to safely and effectively reduce OCD symptoms. They then conducted a prospective multicentre, randomized, double-blind, placebo-controlled trial[31], the results of which showed that patients treated with DTMS had a more significant reduction in OCD symptom scale scores, with an efficacy rate of 38.1%. At the 1-mo follow-up, the efficacy rate increased in both the treatment and sham-stimulation groups, to 45.2% in the treatment group and 17.8% in the sham-stimulation group. In 2018, the United States FDA approved DTMS with the "H7 coil" for the treatment of OCD, potentially for patients for whom medication and psychological interventions have not been effective. Based on previous studies, the response of patients with OCD to DTMS treatment was determined by whether the total score on the Y-BOCS decreased by 30% or more from baseline[32]. We summarised the available studies and found that the remission rate of OCD treated with DTMS was 29.22%-53.90% [31,33,34].

Table 2 Development of deep transcranial magnetic stimulation in obsessive-compulsive disorder

Ref.	Method	Result	Adverse events	Significance
Modirrousta *et al* [30], 2015	1 Hz DTMS stimulates PFC	Improvement in Y-BOCS	Electric shocking sensation	Low frequency deep rTMS was effective in OCD symptom reduction
Carmi *et al*[27], 2018	20 Hz or 1 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Slight headache	DTMS has the ability to directly modify ACC activity
Carmi *et al*[31], 2019	20 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Slight headache	High-frequency DTMS in special region can significantly improve OCD symptoms
Ikawa *et al*[33], 2022	20 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Slight headache	DTMS treatment of OCD had a favorable therapeutic effect
Ikawa *et al*[33], 2022	20 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Electric shocking sensation	DTMS was found to be a safe and effective intervention for OCD symptoms in adolescents

Y-BOCS: Yale-Brown obsessive compulsive scale; mPFC: Medial prefrontal cortex; ACC: Anterior cingulate cortex; DTMS: Deep transcranial magnetic stimulation; PFC: Prefrontal cortex; OCD: Obsessive-compulsive disorder.

Although DTMS is effective in improving OCD symptoms and Y-BOCS scores, the biological basis for the efficacy of DTMS is not yet clear, and more randomised, double-blind, placebo-controlled trials (using dummy coils, at different parameter frequencies) and larger-sample clinical trials are needed to explore this further.

Schizophrenia

SZ, a chronic illness of unknown etiology, is a psychiatric disorder that affects 1% of the world's population[35,36] and may be associated with genetic and environmental risk factors. SZ is often associated with severe impairments in emotions, thinking, and behaviour. A common symptom in people with SZ is hallucinations, which can cause mental debilitation in schizophrenics. Although antipsychotic medications are effective for this symptom, they are still less effective in about 25% of patients. Some studies have shown that hallucinations are associated with increased activity in areas such as the temporal cortex and prefrontal cortex[37], so inhibitory DTMS could be considered to reduce abnormal activity in these areas.

The development of DTMS in SZ is shown in Table 3. DTMS treatment may improve positive symptoms. Rosenberg *et al*[38] conducted an open-label study in which the investigators treated eight patients with SZ diagnosed with persistent hallucinations (hallucinations that had persisted for an average of 11 years) with low-frequency DTMS using an H1 coil, using the Auditory Hallucinations Rating Scale (AHRS) and the Positive Symptom Rating Scale (SAPS) to assess the patients. Five of the patients' AHRS scores decreased by 34.5% and the SAPS score improved by 23.1%. Three patients were subsequently treated with 20 sessions of DTMS, resulting in a 27.8% improvement in AHRS and a 13.75% improvement in SAPS at the end of treatment, and these improvements were maintained over the subsequent 1-mo follow-up period[38]. They then conducted a double-blind study in 2012, in which a total of ten patients completed the treatment and both groups showed an increase in phantom hearing scores, but the difference between the treatment and sham stimulation groups was not statistically significant on either scale[39]. Negative symptoms and cognitive deficits are central to SZ, but current treatments for this condition are underdeveloped. Levkovitz *et al*[40] used DTMS to stimulate the prefrontal cortex of 15 patients with SZ in 2011, and the results obtained 2 wk after treatment showed improvements in both negative symptoms and cognitive function. Some previous studies have suggested that the temporal and parietal cortices are central parts of the language system, that verbal hallucinations may be related to abnormal activity in these regions, and that it may be possible to reduce the hallucination symptoms by suppressing pathological hyperactivity in this region through the use of low-frequency magnetic stimulation[41], but more in-depth studies are needed in the future. In patients with SZ, negative symptoms are often associated with social dysfunction, so it is important to improve negative symptom-based treatment. In 2022, a study of bilateral DTMS of the insula and prefrontal cortex using special H4 coils demonstrated the therapeutic effects of DTMS on psychotic symptoms. In functional magnetic resonance imaging (fMRI) analyses, resting-state connectivity between the insula and the default mode network showed a numerically greater change from baseline in the active DTMS group than in the sham group, consistent with a functional change in insular circuitry[42-44].

Although the current findings on the treatment of negative symptoms with DTMS have shown to be effective, the sample size of the studies is small, and more clinical studies are needed to confirm this in the future. DTMS was also compared to other brain stimulation techniques such as electroconvulsive therapy, transcranial direct current stimulation, vagus nerve stimulation, or standard TMS.

Substance use disorders

Substance use disorders (SUDs) are a group of disorders in which brain damage is caused by chronic use of alcohol and drugs. Substance use disorders are currently difficult to treat, medications are less effective, and the disease has a high relapse rate of 40%-60%[45]. Non-invasive brain stimulation can affect neuroplasticity in the cerebral cortex and throughout the brain, potentially reducing and controlling the compulsive craving for psychoactive substances by rewiring the brain's nerves[46]. Different substance use disorders are affected by similar neural circuits, and because the

Table 3 Development of deep transcranial magnetic stimulation in Schizophrenia

Ref.	Method	Result	Adverse events	Significance
Birdi *et al*[36], 2023	1 Hz DTMS stimulates LTPC	Significant improvement in AHRS score	Transient headache	DTMS treatment was effective for chronic auditory hallucinations in schizophrenic patients
Rosenberg *et al* [38], 2011	20 Hz DTMS stimulates PFC	Cognition and negative symptoms are improved	Transient headache and fatigue	DTMS can improve negative symptoms and cognitive deficits for schizophrenia patients
Rosenberg *et al* [38], 2011	1 Hz DTMS stimulates LTPC	Significant improvement in AHRS score	Mild and self-limiting headaches	DTMS had no significant effect on auditory hallucinations
Rabany *et al*[43], 2014	20 Hz DTMS stimulates PFC	SANS was significantly reduced	Unreported	DTMS was effective for negative symptoms, but the effect was moderate
Linsambarth *et al* [44], 2019	18 Hz DTMS stimulates bilateral PFC	SANS was significantly reduced		DTMS contributed to negative symptoms in schizophrenia
Moeller *et al*[42], 2022	10 HZ DTMS stimulates the insular and prefrontal cortices	The DTMS group had a more pronounced decrease in insula blood flow than the sham operation group	Unreported	DTMS in smoking patients with schizophrenia was effective

AHRS: Auditory Hallucinations Rating Scale; DTMS: Deep transcranial magnetic stimulation; PFC: Prefrontal cortex; SANS: Scale for the Assessment of Negative Symptoms; TPC: Temporoparietal cortex.

use of H-coils can alter the electrical field activity in deep subcortical brain regions, DTMS may be recommended for the treatment of different SUDs.

The evolution of DTMS applied to SUDs is shown in Table 4. Harel *et al*[47] intervened in patients with alcohol use disorders using high-frequency (10 Hz) DTMS and showed that the results were similar to sham. The results showed that the DTMS group had significantly lower levels of alcohol craving and relapse rates of alcohol use disorders compared to the sham-stimulation treatment group. In addition, resting-state network connectivity between the ACC and medial frontal cortex was reduced in the DTMS group during the 3 wk of treatment, and this altered connectivity may be related to substance-induced craving and relapse[47]. Dinur-Klein *et al*[48] evaluated the effects of bilateral prefrontal and insula cortical stimulation using DTMS in patients with nicotine use disorder. The investigators recruited 115 patients with nicotine use disorder (for whom prior treatment had been ineffective), randomizing patients to high-frequency and sham stimulation groups, and showed that high-frequency DTMS treatment significantly reduced patients' nicotine dependence, resulting in a 44% abstinence rate at the end of treatment and a 33% abstinence rate at the 6-mo follow-up, in contrast to the low-frequency DTMS (1 Hz) group, which was less effective[48-50].

In summary, it is clear from the few available studies that high-frequency DTMS may be effective in the acute phase of treatment for some SUD symptoms.

APPLICATION OF DTMS IN NEUROLOGICAL DISEASES

Alzheimer's disease

Alzheimer's disease (AD) is a common and persistent neurological disorder whose prevalence is increasing with the world's aging population. The pathological mechanism of AD may be the structural changes in the brain, abnormal protein deposition, and loss of cholinergic neurotransmission[51]. The functional networks closely related to memory in the brain of AD patients show large-scale disruptions and their plasticity is impaired, as confirmed by neurophysiological and fMRI studies[52]. Currently, there are several disease-modifying therapies such as monoclonal antibodies developed [53]. However, these therapies are specific to early AD stages and amyloid-related imaging abnormalities[54], and there is no effective treatment for AD patients[55]. Gamma oscillations function in information processing by modulating neuronal and glial cell responses to ameliorate AD[56], and pathological increases in gamma band power may be due to the disruption of GABAergic interneuronal networks, resulting in an imbalance between excitation and inhibition in the central nervous system[57]. Brain modulation techniques such as TMS can regulate this unbalanced state of excitation. Recently, brain stimulation to improve cognitive function has received much attention. Chang *et al*[58] first introduced TMS to the motor cortex, and it has now been suggested to be useful in improving cognitive function in AD patients, and the basic principle is that rTMS induces long-term potentiation to enable patients to have enhanced neuronal signaling and increased synaptic plasticity. High-frequency rTMS applied to the dorsolateral prefrontal cortex[59-61] or multiple brain regions[62,63] improves cognition in randomised controlled trials (RCTs) in AD, while functional performance and mood are unaffected[64]. DTMS is still in the early stages of investigation for the treatment of patients with AD.

The evolution of DTMS applied to AD is shown in Table 5. In 2016, Avirame *et al*[65] first applied DTMS to patients with moderate to severe AD, where the researchers used H2 coils to administer 20 DTMS sessions to the PFC of 11 patients with moderate to severe AD, and found that cognitive function improved in 60% to 77% of patients after

Table 4 Development of deep transcranial magnetic stimulation in substance use disorders

Ref.	Method	Result	Adverse events	Significance
Girardi *et al* [49], 2015	20 Hz DTMS stimulates DLFPC	Craving scores dropped significantly	Unreported	DTMS was well tolerated and found to be effective in AUD
Harel *et al* [50], 2022	10 Hz DTMS stimulates mPFC and ACC	A lower percentage of heavy drinking days	Moderate to severe headaches	DTMS was a safe and well-tolerated intervention, with promising initial evidence for efficacy in alcohol addiction

DLFPC: Dorsolateral prefrontal cortex; DTMS: Deep transcranial magnetic stimulation; SUD: Substance use disorders; mPFC: Medial prefrontal; ACC: Anterior cingulate cortices; AUD: Alcohol use disorder.

Table 5 Development of deep transcranial magnetic stimulation in Alzheimer's disease

Ref.	Method	Result	Adverse events	Study design	Significance
Avirame *et al* [65], 2016	10 Hz DTMS for PF stimulation	60%-70% of AD patients' cognitive function was improved	Light headache and occasional tiredness	Case series study	DTMS led to preservation and even improvement of cognitive functions
Leocani *et al* [66], 2020	10 Hz DTMS	ADAS-cog at 4 and 8 wk compared with baseline was improved	Temporary headaches	Double-blind, placebo-controlled pilot study	DTMS was feasible and safe in patients with probable AD

ADAS-cog: Alzheimer's disease assessment scale-cognitive; AD: Alzheimer's disease; DTMS: Deep transcranial magnetic stimulation; PF: Bilateral prefrontal regions.

treatment[65]. A randomized double-blind placebo-controlled trial by Leocani *et al*[66] showed that the DTMS group showed an improvement in AD Assessment Scale-Cognitive (ADAS-cog) scores compared with the sham-stimulation group at weeks 4 and 8 compared with baseline, but this effect diminished after 2 mo of treatment, suggesting that DTMS is effective in AD patients in a short period. However, most of the subjects included in the above two studies were patients with moderate to severe AD for whom DTMS was ineffective in improving cognitive function, and this may be related to the reduced neuroplasticity of the brain in patients with advanced AD. Patients with early AD respond better to DTMS.

Although DTMS is effective in improving cognitive function in AD patients, we need to further validate the efficacy of DTMS combined with cognitive training in early AD patients and conduct more relevant large-scale multicenter RCTs.

Aphasia

Approximately 1/3 of stroke patients are diagnosed with aphasia[67]. Aphasia is an acquired language disorder that has phonological, morphological, semantic, and syntactic deficits that negatively affect patients' functioning, emotions, quality of life, and social participation. Language deficits after stroke aphasia are heterogeneous, and each subtype of aphasia is associated with damage to specific cortical areas, with some extension to subcortical areas[68,69]. Studies have shown that TMS can significantly improve language outcomes in patients with aphasia[70]. H-coil stimulation of a large number of neural networks involved in language function may be more effective than conventional focal coils because of the extensive and non-selective stimulation of language areas in the brain, where aphasia is often due to damage to areas involved in language function[71].

The development of DTMS applied to aphasia is shown in Table 6. First, Spagnolo *et al*[72] utilized repetitive DTMS on a patient diagnosed with progressive supranuclear paralysis accompanied by aphasia. The patient exhibited enhancements across all cognitive domains, particularly in language function. Furthermore, 18-FDG-PET scans revealed notable clinical, neuropsychological, and metabolic improvements when compared to the pre-treatment phase. These findings suggest that DTMS elicits excitation in pertinent functional circuits beyond the intended area of stimulation. Moreover, the observed improvements endured for a minimum of 1 mo post-stimulation, as confirmed through telephone follow-up. In the same year, Trebbastoni *et al*[73] treated a patient with primary progressive aphasia with high-frequency DTMS in the left dorsolateral PFC and showed that the patient also showed transient but significant improvements in verbal fluency and writing ability. Chieffo *et al*[71] suggested that high-frequency DTMS can significantly improve naming ability in patients with chronic post-stroke aphasia.

Although the sample sizes of all the above studies are small and subject to some error, they provide new insights into the use of DTMS in aphasia.

Post-stroke motor dysfunction

Limb motor dysfunction is one of the most common sequelae after stroke. rTMS has been studied to improve motor dysfunction in stroke patients, but the results are somewhat mixed. Some scholars have suggested that an interhemispheric competition model is a basis for rTMS to promote motor recovery after stroke, in which the healthy hemisphere inhibits the diseased hemisphere, resulting in reduced dominance of the hemiplegic limb[74]. In recent years, some of the

Table 6 Development of deep transcranial magnetic stimulation in aphasia

Ref.	Method	Result	Adverse events	Significance
Spagnolo *et al*[72], 2013	10 Hz DTMS stimulates Broca's area and DLPFC	Improvement of language function	Unreported	This observation opens new possibilities for treatment of drug-unresponsive neurodegenerative disorders
Trebbastoni *et al*[73], 2013	hf-rTMS stimulates DLPFC	Improved language in LPPA	Unreported	DTMS improved the linguistic skills
Chieffo *et al*[71], 2014	10 Hz DTMS stimulates Broca's area	Significant improvement in the naming power	Unreported	Deep brain rTMS improved naming in right-handed chronic poststroke aphasic patients

LPPA: Primary progressive aphasia logopenic variant; DLPFC: Dorsolateral prefrontal cortex; DTMS: Deep transcranial magnetic stimulation; hf-rTMS: High frequency-repetitive transcranial magnetic stimulation; rTMS: Repetitive transcranial magnetic stimulation.

above-mentioned scientists have critically proposed a bimodal balance-recovery model, suggesting that the residual structural reserve of the corticospinal tract on the affected side also influences both the hemispheric balance and the degree of functional recovery. Diffusion tensor imaging studies have shown that the integrity of nerve fiber connections between primary and secondary motor areas is positively correlated with recovery of motor function after stroke[75]. DTMS helps to improve motor dysfunction after a stroke.

The development of DTMS applied to post-stroke motor dysfunction is shown in Table 7. Chieffo *et al*[76] applied DTMS to patients with lower limb motor dysfunction after chronic stroke, showing improved lower limb function in patients receiving treatment, and high-frequency DTMS has long-term effects on lower limb motor function in patients with chronic stroke. In 2018, this team again applied DTMS to the rehabilitation of upper limb motor dysfunction after chronic stroke and found that the recovery of upper limb function in patients treated with DTMS combined with exercise training was significantly better than that in patients treated with exercise training combined with sham stimulation, and this effect was more pronounced in patients with severe upper limb motor dysfunction, without serious adverse effects [77].

DTMS is effective in restoring motor function in the limbs after stroke, but the exact mechanism of action remains to be explored. Does DTMS somehow improve the language of patients with aphasia? At this time, we have not found any studies to provide a reference. Existing studies show clinically beneficial effects of TMS with or without combined speech and language therapy on overall language function and expressive language (including naming, repetition, writing, and comprehension) in patients with post-stroke aphasia[70]. In the assessment of aphasia and why not in aphasia therapy, spontaneous and semi-spontaneous speech analysis may be useful[78]. We recommend that future DTMS research on aphasia could be more involved in this gap area.

PD

PD is the second most common neurodegenerative disease in the world, and patients most commonly suffer from abnormal motor symptoms due to the loss of dopaminergic neurons in the substantia nigra[79]. The gold standard treatment for PD is oral levodopa, but the long-term efficacy of levodopa is mostly not maintained[80]. Some reports suggest that the excitability of cortical-mediated pathways may be altered in PD patients, resulting in dyskinesia[81]. Several studies have shown that stimulation of the motor cortex with high-frequency rTMS can improve dyskinesia in PD patients and that the effects can be sustained for a longer period of time[82]. However, some studies suggest that cortical inhibition is impaired in PD patients[83] and perhaps low-frequency stimulation may be more beneficial for PD patients, whereas DTMS is used to act on a wider range of cortical and deeper brain areas.

The development of DTMS applied to PD is shown in Table 8. In 2013, by treating 27 PD patients with movement and high-frequency rDTMS to the prefrontal cortex, Spagnolo *et al*[84] found that the Unified PD Scale (UPDRS) score of PD patients improved significantly after treatment compared to before treatment. Spagnolo *et al*[85] conducted a randomized, sham-controlled trial to evaluate whether high-frequency TMS with an H5 coil is safe and effective for PD patients, and the results showed that patients who received rTMS (M1-PFC and M1 combination) had better results in tremor and hemilateral scores than those in the sham stimulation group. There was no significant difference in safety and efficacy between the two groups, suggesting that gh-frequency rTMS with the H-coil is a safe and effective intervention. It has been suggested that high-frequency rTMS acting on the M1 or PFC may, on the one hand, induce the release of endogenous dopamine in the ipsilateral dorsal striatum[86]. On the other hand, it may promote the production of dopaminergic neurons[87-90].

Studies today have shown that PD patients tolerate DTMS well and no serious adverse effects have been reported in these patients, but there are still some side effects such as transient headache, dizziness, and involuntary movements. However, DTMS can be used to improve the symptoms of dyskinesia in PD patients, and high-frequency stimulation may be more effective than low-frequency stimulation. In the future, RCTs with larger sample sizes and long-term follow-up are needed to determine the optimal treatment parameters and duration of the effect of DTMS.

Table 7 Development of deep transcranial magnetic stimulation in post-stroke motor dysfunction

Ref.	Method	Result	Adverse events	Significance
Chieffo *et al* [76], 2014	20 Hz DTMS	Significant improvement in lower limb motor function	Unreported	DTMS could induce improvements in lower limb functions in the chronic post-stroke period
Chieffo *et al* [77], 2018	20 Hz DTMS	Upper limb motor function improved significantly	Transitory dizziness, toothache, and muscle twitches	DTMS combined with exercise training is more effective (upper limb motor function)

DTMS: Deep transcranial magnetic stimulation.

Table 8 Development of deep transcranial magnetic stimulation in Parkinson's disease

Ref.	Method	Result	Adverse events	Significance
Spagnolo *et al* [84], 2014	10 Hz DTMS for PF stimulation	UPDRS was improved	Slight and transitory hypotension and headache	DTMS might be a safe treatment for PD motor symptoms
Cohen *et al*[87], 2018	M1 + PFC or M1	M1 + PFC OR M1 group was improved in T-UPDRS and M-UPDRS	Mild and transient head discomfort, transient fatigue, and rare mild visual transient hallucinations during stimulation	DTMS improved PD motor symptoms but the effect was moderate
Torres *et al*[80], 2015	M1 + PFC	UPDRS was improved	Sleepiness, headaches, and nausea	DTMS improved motor, postural, and motivational symptoms of PD patients
Cohen *et al*[88], 2016	1 Hz DTMS M1 and 10 Hz DTMS PFC	UPDRS was improved	Headache, dizziness, pain in the head or neck during treatment; nausea, general weakness, and transient aggravation of gait disturbance	DTMS improved motor, but no advantage compared to sham treatment
Spagnolo *et al* [85], 2020	M1 + PFC or M1	UPDRS was improved	Mild, not-distressing, and transient dyskinesias	DTMS was a safe and potentially effective procedure
Cohen *et al*[87], 2018	1 Hz M1 or 10 Hz PFC	UPDRS was improved	Headache, nausea, and discomfort of the eye region or tearing of the eyes during stimulation	DTMS can decrease the subjective motor symptom severity and depression

PF: Bilateral prefrontal regions; M1 + PFC: Sequential stimulation of low frequency over the primary motor cortex and then high frequency over the prefrontal cortex; M1: Low-frequency stimulation over the primary motor cortex alone; UPDRS: Unified Parkinson's Disease Rating Scale; M-UPDRS: Motor UPDRS; T-UPDRS: Total UPDRS; DTMS: Deep transcranial magnetic stimulation; PFC: Prefrontal cortex; PD: Parkinson's disease.

DISCUSSION

The results of our review suggest that the DTMS technique is safe and effective when applied to various neurological and psychiatric disorders, with no serious adverse effects identified other than transient headache and fatigue. However, the biology of the efficacy of DTMS is not yet clear, so its efficacy is mostly assessed by psychometric scales such as the UPDRS and HDRS-24[13], and biological indicators are lacking. A comparison of DTMS with other brain stimulation techniques[90] such as magnetic shock therapy, electroconvulsive therapy[91], transcranial direct current stimulation, vagus nerve stimulation, or deep brain stimulation would provide better clinical evidence for patients.

The advantage of DTMS over conventional TMS is that the H-coil can stimulate deeper areas of the brain without increasing the intensity of the stimulation[92], thus ensuring the continuous stimulating effect of DTMS. There are currently more than 20 H-coils available, of which the H1/H2 coil is FDA cleared for bilateral PFC stimulation. DTMS can stimulate deeper and wider areas of the brain and modulate neurological function through the H-coil, which is effective and safe in the treatment of PD, AD, SZ, and depression. Based on the above tables, it can be seen that DTMS is currently most commonly used in PD, OCD, and depression, with high levels of patient acceptance and efficacy. Some of the other neurological and psychiatric disorders treated with DTMS are still in the early stages of research, and although some have shown significant efficacy, more research is needed to validate them in the future. It is believed that with the continued optimization of the DTMS coil device and further understanding of the etiology of neurological and psychiatric disorders, as well as the resolution of some ethical and legal issues related to these disorders, the use of DTMS with different coils and parameters for different disorders can be explored in the future, thus creating a standardized treatment plan for patients with different disorders, which will facilitate the treatment of patients who have failed or cannot take medication for a long time. This will facilitate the use of DTMS for patients who have been on medication for a long time or are unable to take medication.

CONCLUSION

A large number of studies have shown that DTMS technology is generally safe and tolerable, with mild side effects, and can be used to rehabilitate mental and nervous system disorders. DTMS regulates neural function by directly stimulating deeper and wider brain regions, and currently the evidence for DTMS in the treatment of depression and OCD should be strong. However, for other neurological disorders (particularly neurodegenerative disorders), there are very preliminary results and small sample sizes. RCTs with larger sample sizes should be warranted.

However, DTMS research is still in the exploratory stage, and several issues need to be addressed and determined: (1) Consistency of efficacy: Although some studies have shown that DTMS is effective in certain diseases, the results of these studies are variable and the effects are unpredictable. Further studies are needed to determine the consistency of efficacy and to identify patients who are best suited for this treatment modality; (2) Long-term safety and side effects: The long-term safety and potential side effects of DTMS are not fully understood, and although some studies have shown that the technique is relatively safe and well tolerated in the short term, the potential for adverse effects and potential risks associated with long-term use needs to be further evaluated; (3) Determining optimal stimulation parameters: DTMS involves the selection of stimulation site, stimulation frequency, stimulation intensity, and other parameters; it is unclear which stimulation parameters are most effective, and further research is needed to determine the optimal stimulation parameters and to ensure their consistency and reproducibility in clinical applications; (4) Disease-specific mechanism of action: The mechanism of action of DTMS on various diseases is not fully understood. A deeper understanding of its mechanism of action may help us to better understand and optimize its clinical application; and (5) Development of individualized therapeutic strategies: Since each patient's situation is unique, there is a need to develop methods for individualized therapeutic strategies that can better guide treatment and improve treatment efficacy by combining information from brain imaging technology and biomarkers. Addressing and identifying these issues will advance the use of DTMS in clinical practice and provide more effective options for the treatment of psychiatric and neurological disorders.

FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Hippocampus protection from apoptosis by Baicalin in a LiCl-pilocarpine-induced rat status epilepticus model through autophagy activation

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Abstract

BACKGROUND

Autophagy is associated with hippocampal injury following status epilepticus (SE) and is considered a potential therapeutic mechanism. Baicalin, an emerging multitherapeutic drug, has shown neuroprotective effects in patients with nervous system diseases due to its antioxidant properties.

AIM

To investigate the potential role of autophagy in LiCl-pilocarpine-induced SE.

METHODS

The drugs were administered 30 min before SE. Nissl staining showed that Baicalin attenuated hippocampal injury and reduced neuronal death in the hippocampus. Western blotting and terminal deoxynucleotidyl transferase dUTP nick end labeling assay confirmed that Baicalin reversed the expression intensity of cleaved caspase-3 and apoptosis in hippocampal CA1 following SE. Furthermore, western blotting and immunofluorescence staining were used to measure the expression of autophagy markers (p62/SQSTM1, Beclin 1, and LC3) and apoptotic pathway markers (cleaved caspase-3 and Bcl-2).

RESULTS

Baicalin significantly upregulated autophagic activity and downregulated mitochondrial apoptotic pathway markers. Conversely, 3-methyladenine, a

commonly used autophagy inhibitor, was simultaneously administered to inhibit the Baicalin-induced autophagy, abrogating the protective effect of Baicalin on the mitochondrial apoptotic level.

CONCLUSION
We illustrated that Baicalin-induced activation of autophagy alleviates apoptotic death and protects the hippocampus of SE rats.

Key Words: Baicalin; Status epilepticus; Autophagy; Mitochondrial apoptosis

Core Tip: This study established the rat model of status epilepticus by intraperitoneally injecting LiCl-pilocarpine. Then, Baicalin was administered to the rats for treatment. The pathological changes of hippocampal were observed. Western blotting and terminal deoxynucleotidyl transferase dUTP nick end labeling assays were used to verify the inhibitory effect of Baicalin on apoptosis of rat hippocampal neuronal cells. We have drawn the conclusion that Baicalin protects the hippocampus from apoptosis.

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INTRODUCTION

It has been reported that 1% of the global population is affected by epilepsy, which has diverse etiologies and is characterized by recurrent and spontaneous seizures[1,2]. The most notable kind of epilepsy is temporal lobe epilepsy, characterized by a typical seizure that originates from the hippocampus-a structure located in the mesial temporal lobe[3-5]. Hippocampal injury following status epilepticus (SE) is due to oxidant damage. The accumulation of reactive oxygen species can harm hippocampal neurons, inducing cell death through an apoptotic or necrotic pathway, as hippocampal cells are highly sensitive to oxidative stress[6].

Autophagy is a highly conserved intracellular process that can be categorized into three classes: Macroautophagy, chaperone-mediated autophagy, and microautophagy. As the major type of autophagy, macroautophagy (hereinafter referred to as "autophagy") is crucial for eliminating cytoplasmic materials and maintaining intracellular homeostasis under pathological conditions[7,8]. This process of degrading long-lived proteins and cytoplasmic organelles is associated with SE, PD, and other neurodegenerative diseases[9]. Indications of autophagy variation have been observed in several neuroprotective drugs (*e.g.*, 17-allylamino-demethoxygeldanamycin and Tanshinone IIA), which simultaneously confirmed their ability to ameliorate SE-induced hippocampal neuronal death by upregulating autophagy[10,11]. Baicalin, as a natural extract, undergoes a safe and established preparation process and offers several significant advantages, including minimal side effects.

Baicalin-a traditional Chinese medicine-is among the main flavonoid compounds isolated from *Scutellaria baicalensis* Georgi and possesses multiple pharmacological properties, including neuroprotective[12], anti-inflammatory[13], antiapoptotic[14], and antioxidant[15] effects. Baicalin can freely cross the blood-brain barrier[14,16]; thus, it has been used to treat many nervous system diseases. Several studies have explored the relationship between autophagy and Baicalin. For example, Baicalin has been found to induce autophagy in tubercle bacillus-infected macrophages through the PI3K/Akt/mTOR signaling pathway, indicating its potential to alter disease progression by regulating autophagy activity[17]. Baicalin has also been shown to exert anticancer and anti-inflammatory effects by activating autophagy in pathogenic cells, such as human bladder cancer T24 cells, human hepatocellular carcinoma SMMC-7721 cells[18], and *Mycobacterium tuberculosis*-infected macrophages. A much-debated issue is whether Baicalin exerts neuroprotective effects while regulating autophagy. However, the mechanism by which Baicalin activates autophagy in the hippocampus following SE remains unclear. Thus, we aim to investigate the emerging role of autophagy in the hippocampus during SE and elucidate the precise mechanism underlying the neuroprotective effects of Baicalin.

MATERIALS AND METHODS

Animal preparation

Ninety-six pathogen-free Wistar rats (male, 180-220 g) were purchased from Shanghai Laboratory Animal Center. The rats were raised under controlled conditions with a 24 °C ± 1 °C temperature and a 12-h light/dark cycle. All rats had free access to water and food.

Rat model of SE and experimental groups

The rat model of SE was induced by intraperitoneally injecting adult Wistar rats with LiCl-pilocarpine[19]. The rats were lightly anesthetized through isoflurane inhalation and then intraperitoneally injected with 0.2 mL (127 mg/kg) of lithium chloride; Pilocarpine (30 mg/kg) was injected 16 h after LiCl administration. Rats that did not develop SE after the injection were excluded. The rats were randomly divided into four groups: Control, SE, SE + B100, and SE + B200 (Figure 1).

For the SE group, pilocarpine (25 mg/kg) was injected intraperitoneally 30 min after intraperitoneal injection of atropine methyl nitrate (2 mg/kg) to ameliorate peripheral cholinergic signs. The control group received a physiological salt solution instead of pilocarpine. The SE + B100 and SE + B200 groups were intraperitoneally injected with 100 mg/kg and 200 mg/kg of Baicalin, respectively, after the pilocarpine injection. The drug dosages used in this study were based on previous reports[20].

3-Methyladenine (3-MA) was used to inhibit autophagy. Subsequently, the rats were randomly divided into the following groups: Control, SE, SE + Baicalin, and SE + Baicalin + 3-MA. In the SE + Baicalin + 3-MA group, rats were injected with 400 nmoL 3-MA (2 μL) through an intracerebroventricular injection to the right lateral ventricle 1 h before SE induction, according to a previous study[21]. The SE + Baicalin and SE + Baicalin + 3-MA received a dose of 200 mg/kg of Baicalin. Isoflurane inhalation was used for anesthesia after SE induction. All rat brains were harvested for subsequent histological and biochemical studies.

Nissl staining

Twenty-four rats were executed 24 h after the onset of SE. HE staining was performed to detect damaged neurons in the hippocampus (six per group) based on a previous study[22]. Damaged neurons were characterized by an abnormal neuronal morphology, a dried-up cytoplasm with vacuoles, and a shrunken- hyperchromatic nucleus, as reported in a previous study[23].

Transferase dUTP nick end labeling staining

Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining was conducted using an *in situ* cell death detection kit (Promega) to detect the cell apoptosis index. Briefly, rats were executed 24 h after the onset of SE, and 4-μm-thick coronal slices of the brain tissue were prepared using a paraffin slicer. Proteinase K (Nanjing Jianchen Co., Ltd.) was used to digest the coronal sections for 15 min. After deparaffinization, rehydration, and washing (with PBS), the sections were cultivated with a TdT reaction mix (Promega) containing TUNEL reaction fluid for 50 min at 37 °C (avoiding exposure to light from hereon). To stop the reaction, plastic coverslips were removed, and coronal slides were immersed in 2XSSC (Nanjing Jianchen Co., Ltd.) for 15 min. After three washes with 0.02 M TBS (5 min/wash), the liquid around the sections was dried, and the tablets were sealed with a seal containing DAPI fluorescent dye. Under a fluorescence microscope, localized apoptotic cells appeared green, and DAPI-stained nuclei appeared blue. Five slides per rat and five random fields per slide (scale bar = 50 μm) were selected to calculate the final average percentage and apoptosis index.

Western blotting

Hippocampal tissues were isolated, and hippocampus protein was extracted. The protein content was calculated using the BCA assay. Each quantity of protein per lane (30 μg) was separated on a 12% SDS-PAGE gel. The proteins were then electrotransferred onto a PVDF membrane (Millipore, United States). The membrane was blocked with 5% skim-fat milk prepared with TBST for 3 h. Primary antibody incubation was conducted with the following antibodies: LC3B (1:1000, Cell Signaling Technology), Beclin 1 (1:2000, Cell Signaling Technology), p62/SQSTM1 (1:500, Cell Signaling Technology), cleaved caspase-3 (1:500 dilution, Cell Signaling Technology), Bcl-2 (1:500 dilution, Cell Signaling Technology), and β-actin (1:2000, Bioworld Technology). Subsequently, secondary antibody incubation was conducted for 3 h at room temperature. The signals were visualized using an ECL reagent (Millipore), and band density was quantitatively analyzed using Quantity One software. The expression intensity was normalized to the loading control (β-actin).

Immunofluorescent labeling

Immunofluorescence staining was performed to localize LC3 in the hippocampal cells. Brain sections from 24 rats (six per group) were prepared as described for the TUNEL staining procedure.

The slides were blocked with 5% normal donkey serum containing 0.01% Triton X-100 for 2 h. Primary antibody incubation was conducted with antibodies against LC3B (1:1000, Cell Signaling Technology) for 12 h at 4 °C. After washing three times with PBST, the sections were incubated with the secondary antibody (1:200, Alexa Fluor 594) for 2 h. DAPI treatment was applied for 1 min, and the sections were analyzed under a fluorescence microscope. We counted the cells with LC3 puncta, which appear as a result of LC3-II aggregation around the nucleus, and positive cells in the same field of view were quantified. In each coronal section, six fields (scale bar = 50 μm) around the hippocampus were randomly chosen to determine the average.

Statistical analysis

All results were represented as mean ± SD. The GraphPad Prism 6 software was used to analyze the data. Analysis of variance was used to compare data among multiple groups. Inspection level $\alpha = 0.05$ and $P < 0.05$ was considered a statistical difference.

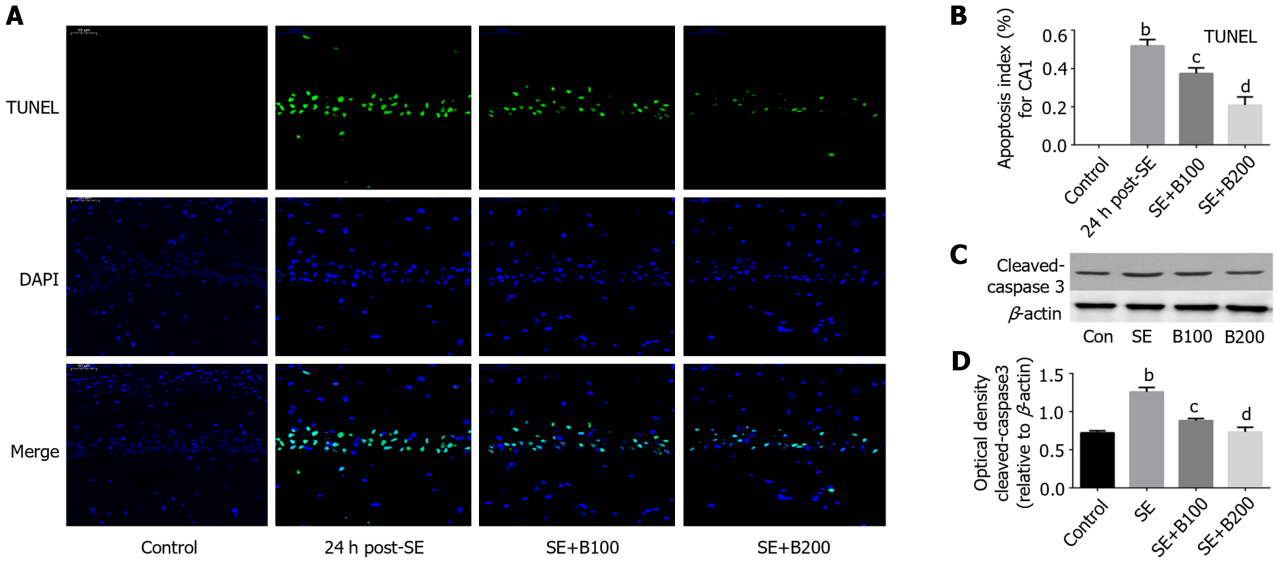

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Figure 1 Baicalin ameliorated status epilepticus-induced neuronal apoptosis. A: Transferase dUTP nick end labeling staining was performed; B: Neuronal apoptosis was analyzed; C: Western blotting was performed; D: Semi-quantitative analysis of cleaved caspase-3 (n = 6). $^{b}P < 0.01$ compared to the control group; $^{c}P < 0.05$ and $^{d}P < 0.01$ compared to the status epilepticus group. Scale bar = 50 μm. SE: Status epilepticus; TUNEL: Transferase dUTP nick end labeling.

RESULTS

Baicalin exerted neuroprotective effects on the hippocampus following SE

Because the neurons in hippocampal CA1 are sensitive to SE stress, toluidine blue staining was performed to detect neuronal loss. The number of surviving neurons was significantly lower in the SE group than in the control group. However, Baicalin significantly increased the number of surviving neurons after SE (Table 1). To further confirm whether Baicalin provides neuroprotection to the hippocampus in SE rats, we monitored the latency of seizures following pilocarpine administration. The latent period (the time from pilocarpine administration to the onset of a seizure above the grade of Racine IV) was 29.60 ± 6.603 min in the SE group, whereas it was 41.70 ± 10.93 min and 63.80 ± 11.73 min in the Baicalin intervention groups (SE + B100 and SE + B200 groups, respectively). Treatment with different doses of Baicalin significantly prolonged the latency, and these differences were statistically significant ($P < 0.01$). The seizure latency in the SE + B200 group exceeded that in the SE + B100 group (Table 2). These results indicate that both concentrations of Baicalin exerted neuroprotective effects on the hippocampus dose-dependently. Therefore, the dosage of Baicalin (200 mg/kg) that produced superior effects was selected and employed for the subsequent experiments.

Baicalin reduced neuronal apoptosis in the hippocampus of SE rats

SE induced significant apoptosis of neurons in hippocampal CA1 ($P < 0.01$; Figure 1A and B). However, after 24 h, the apoptosis percentage was considerably lower in the SE + B100 and SE + B200 groups than in the SE group, with the SE + B200 group showing a more significant decrease (Figure 1B).

The level of pro-apoptotic cleaved caspase-3 in the SE + B200 group was significantly lower than in the SE group ($P < 0.01$; Figure 1C and D). These findings confirmed that Baicalin has neuroprotective effects against SE-induced apoptosis in an SE rat (Figure 2).

Baicalin upregulated autophagy in hippocampal neurons

To further investigate the potential relationship between autophagy and the neuroprotective effect of Baicalin, we measured three highly related autophagy proteins (p62/SQSTM1, Beclin 1, and LC3) as markers of autophagy using western blotting[24]. Under normal conditions, LC3 exists in a cytosolic form (LC3-I), whereas during autophagy activation, LC3-I is cleaved, lipidated, and inserted into autophagosome membranes as LC3-II. Beclin 1, located in the trans-Golgi network, contributes to autophagosome formation and localizes autophagy-related proteins in the pre-autophagosome membrane. p62, an important factor in cytoplasmic material delivery, is also degraded by autophagy and thus frequently serves as an autophagy marker.

As shown in Figure 3A-D, Beclin 1 and LC3-II levels were lower in the SE group than in the control group, whereas the level of p62 was significantly higher in the SE group. These results indicate that SE insults can partially inhibit autophagy activity. However, Baicalin treatment significantly upregulated the levels of Beclin 1 and LC3-II and downregulated the level of SQSTM1/p62 compared with the SE group, indicating that Baicalin activates autophagy in the pilocarpine-induced SE rat model. The results of immunofluorescence staining are consistent with those of western blotting (Figure 3). The SE group exhibited a slight decrease in the number of cells with LC3 puncta (Figure 4A). Moreover, Baicalin significantly enhanced the number of LC3-positive cells compared to the group SE (Figure 4B).

Table 1 Protective effect of Baicalin against neuron death in the hippocampal CA1 area following status epilepticus

Group	Neuron numbers (mean ± SD)
Control	129.0 ± 11.0
24 h post-SE	29.60 ± 6.603[a]
24 h post-SE + B100	41.70 ± 10.93[b]
24 h post-SE + B200	63.80 ± 11.73[c]

[a]$P < 0.01$ compared with the control group.
[b]$P < 0.01$ compared with the 24 h post-SE group.
[c]$P < 0.001$ compared with the 24 h post-SE group.
Data are represented as mean ± SD ($n = 6$). Under a light microscope, the surviving neurons showed regular cell morphology and round nuclei. Neuron number is expressed as the number of surviving neurons/0.5-mm-long hippocampal CA1 subfield. SE: Status epilepticus.

Table 2 Neuroprotective effect of Baicalin on seizure latency

Group	Seizure latency (mean ± SD), min
Control	
24 h post-SE	29.60 ± 6.603
24 h post-SE + B100	41.70 ± 10.93[a]
24 h post-SE + B200	63.80 ± 11.73[b]

[a]$P < 0.01$ compared with the 24 h post-status epilepticus (SE) group.
[b]$P < 0.001$ compared with the 24 h post-SE group.
Data are represented as mean ± SD ($n = 6$). SE: Status epilepticus.

Methyladenine inhibited the autophagy activated by Baicalin and abrogated its protective effect against the apoptotic pathway

To further explore the correlation between Baicalin-induced autophagy and apoptosis following SE, we applied 3-MA to detect alterations in autophagy proteins through western blotting. LC3-II and Beclin 1 levels were significantly lower in the SE + B + 3-MA group than in the SE + B group (Figure 3B and C). Conversely, the level of p62 was higher in the SE + B + 3-MA group than in the SE + B group (Figure 3D). These results indicate that normal baseline autophagy is possibly inhibited by SE and that Baicalin-induced autophagy is abolished by 3-MA.

Activated caspase-3 degrades the substrate, and the degradation products enhance mitochondrial permeability, ultimately resulting in apoptosis. Bcl-2 can reportedly suppress apoptosis by inhibiting the activation of caspase-3, which is released in the upstream and downstream apoptotic pathways. To further investigate the mechanism underlying the neuroprotective effect of Baicalin following SE, we evaluated mitochondrial apoptosis–related proteins using western blotting (Figure 3E-G).

The level of Bcl-2 was lower in the SE group than in the control group, whereas the level of cleaved caspase-3 was significantly higher in the SE group than in the control group ($P < 0.01$; Figure 3E-G). Therefore, SE stress could induce neuronal apoptosis in the hippocampus, possibly through the regulation of mitochondrial apoptosis-related proteins. Furthermore, Baicalin restored Bcl-2 levels and reduced the level of cleaved caspase-3 compared with the SE group, suggesting that Baicalin ameliorated SE-induced mitochondrial apoptosis. In addition, 3-MA significantly increased mitochondrial apoptosis by enhancing cleaved caspase-3 and abrogating the restoration of Bcl-2 induced by Baicalin. Overall, these results illustrate that 3-MA exacerbated mitochondrial apoptosis in SE and abrogated the neuroprotective effect of Baicalin against the apoptotic pathway.

DISCUSSION

SE is a complex pathophysiological process involving multiple mechanisms. Baicalin is a traditional herbal medicine with multitarget protective effects against seizures[25]. A previous study in our laboratory found that Baicalin has a neuroprotective effect on the hippocampus following SE through the antiapoptotic pathway. However, the correlation between autophagy and the effects of Baicalin remained unclear.

To further investigate the function of Baicalin after SE, we monitored seizure latency and apoptosis in this study. The most significant finding (using western blotting and immunofluorescence) was that Baicalin promoted autophagy activity and inhibited mitochondrial apoptosis following SE. Furthermore, the intervention of 3-MA inhibited Baicalin-induced autophagy and even abolished its neuroprotective effects against mitochondrial apoptosis. These findings have

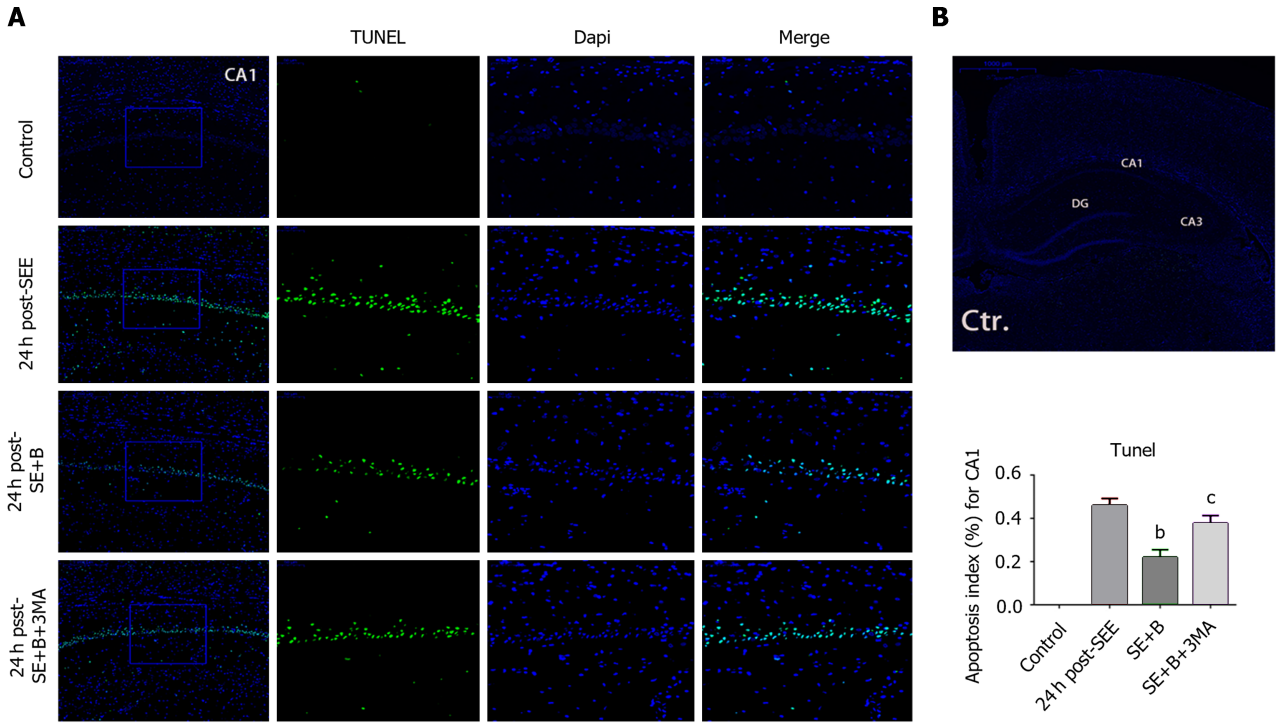

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Figure 2 Baicalin ameliorated status epilepticus-induced neuronal apoptosis. A: Transferase dUTP nick end labeling staining was performed; B: Neuronal apoptosis was analyzed. Baicalin protects the hippocampus from apoptosis following status epilepticus (SE), and 3-Methyladenine reverses Baicalin-induced neuroprotection in hippocampal neurons. Data are represented as mean ± SD. (n = 5), $^{b}P < 0.01$ *vs* the SE group; $^{c}P < 0.05$ *vs* the SE + B group. Scale bar = 50 μm. SE: Status epilepticus; TUNEL: Transferase dUTP nick end labeling; 3-MA: 3-Methyladenine.

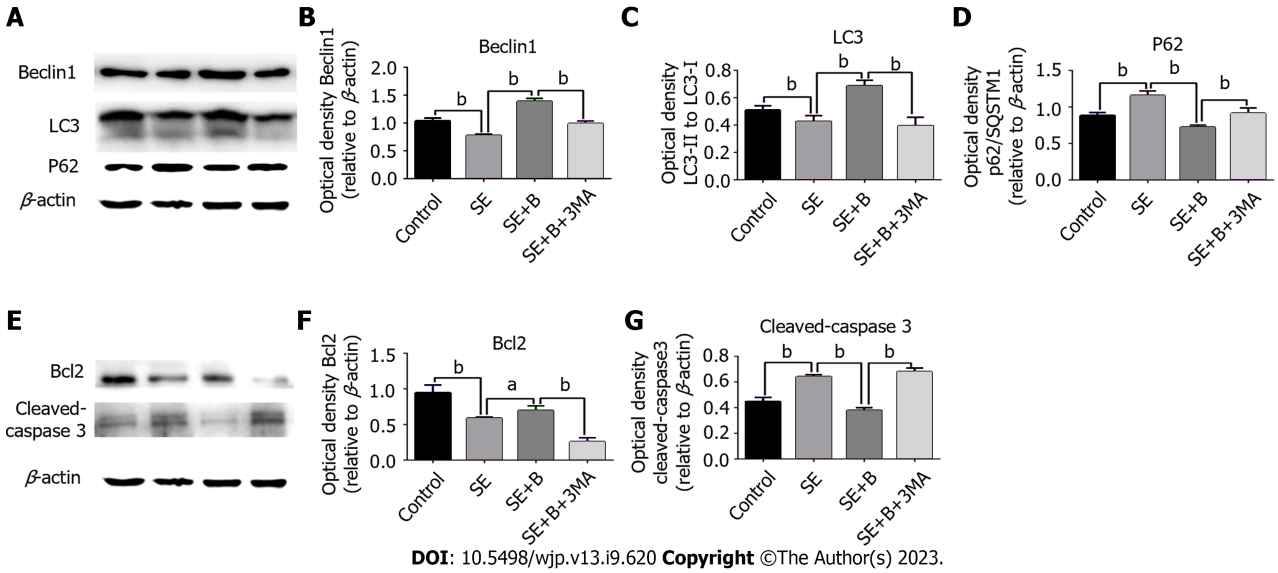

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Figure 3 The autophagy markers (p62/SQSTM1, Beclin 1, and LC3) and apoptotic pathway markers (cleaved caspase-3 and Bcl-2) were measured using western blotting. A: The autophagy markers (p62/SQSTM1, Beclin 1, and LC3) were measured using western blotting; B: The expressions of Beclin 1; C: The expressions of LC3; D: The expressions of p62; E: The apoptotic pathway markers (cleaved caspase-3 and Bcl-2) were measured using western blotting; F: The expressions of Bcl-2; G: Cleaved caspase-3 were analyzed. n = 6. $^{a}P < 0.05$ and $^{b}P < 0.01$. SE: Status epilepticus; 3-MA: 3-Methyladenine.

theoretical implications for the treatment of epilepsy by regulating autophagy.

In recent decades, the focus on alterations in autophagy after SE has increased due to the close relationship between autophagy activity and hippocampal injury. Different theories regarding the role of autophagy in nervous system diseases exist in the literature. The prevailing view is that activated autophagy has a protective role in rat models of ischemia-reperfusion[26-29], but there is still some ambiguity. A previous study focusing on autophagy has noted that autophagy dynamics in a rat's hippocampus act as determinants for epileptogenesis, suggesting that applying autophagy

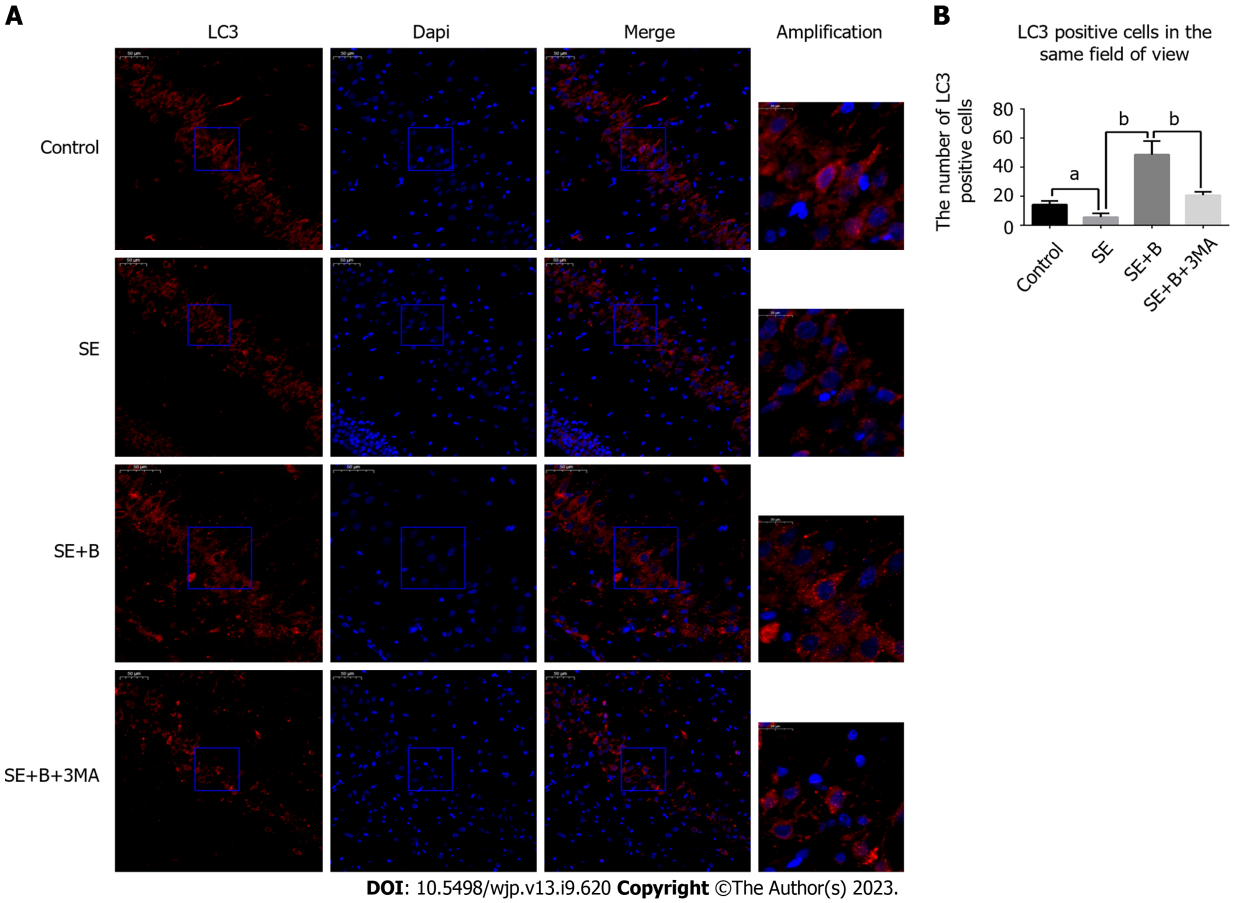

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Figure 4 The number of LC3-II-positive neurons was partially decreased by SE and increased by Baicalin. 3-Methyladenine **reversed the Baicalin-induced alteration.** A: Representative immunofluorescence staining; B: Positive neuronal cells were analyzed. $n = 6$. $^{a}P < 0.05$ and $^{b}P < 0.01$ *vs* the relevant group. The number of LC3-II-positive cells/0.5-mm-long subfield of the hippocampus under a light microscope was regarded as the numerical value (scale bar = 50 μm). SE: Status epilepticus; 3-MA: 3-Methyladenine.

inducers such as rapamycin, an mTOR inhibitor, to activate autophagy has an unambiguous effect on severe epileptic seizures[30,31]. Similarly, several studies have supported the view that activating autophagy through specific factors could provide neuroprotection in rat models of epilepsy[32], suggesting that autophagy induction plays a positive role in cell survival.

One significant finding is the activation of autophagy using recombinant human erythropoietin, which has been recently confirmed to exert neuroprotective effects and help ameliorate apoptosis in hippocampal neurons after SE[33]. In our study, we showed that Baicalin treatment significantly upregulated autophagy activity based on alterations in autophagy-related proteins and immunofluorescence staining of LC3-II puncta. In addition, decreased neuronal apoptosis and prolonged seizure latency were observed in Baicalin-treated groups, consistent with the findings of previous studies that support the neuroprotective effect of autophagy on the hippocampus in patients with seizures. A prior report concluded that impaired autophagy possibly contributes to epileptogenesis, which may be interesting as a potential therapeutic target for treating and preventing epilepsy[34]. Nevertheless, we could not elucidate whether autophagy inhibition promotes the occurrence of epilepsy, which is a limitation of our study.

There are possible situations where autophagy plays a dual role in epilepsy. The practical effect of autophagy depends on the degree of its activation due to the release of various deleterious factors following SE. The possible situations are as follows: (1) Inhibited autophagy potentially contributing to epileptogenesis, although a definitive causal relationship between autophagy and epileptogenesis in rat models has not been established; (2) Proper activation of autophagy benefiting the survival of hippocampal neurons by generating adenosine triphosphate; and (3) SE causing autophagic death and apoptosis in hippocampal neurons due to excessive autophagy[35].

It has not been determined whether administering neuroprotective drugs increases or decreases autophagic flow. For instance, we can only detect signs of decreased autophagy because the activation of autophagy promotes the clearance of autophagosome accumulation[36]. However, the amelioration of apoptosis by autophagy activation in epilepsy is complex and has not been fully elucidated.

Pro-apoptotic materials, such as damaged mitochondria and Bax accumulation induced by traumatic brain injury, can be eliminated by increased autophagy flux[37].

A previous study reported another possible mechanism involving autophagy activation and sequestration of abnormal proteins that trigger endoplasmic reticulum (ER) stress[38]. Hence, autophagy activation may inhibit ER stress in response to external stimuli and ameliorate apoptosis[39]. However, the role of autophagy in apoptosis after SE remains

unknown.

In this study, we discovered that Baicalin induces autophagy activation and alleviates apoptosis in hippocampal neurons following SE. Significantly, the abolition of Baicalin-induced autophagy and its neuroprotective effects against the mitochondrial apoptotic pathway by 3-MA administration suggest that autophagy activation may reduce neuronal apoptosis by removing damaged mitochondria after SE.

These results further support previous studies that have linked mitophagy, apoptosis, and neuron survival[34] and reported that mitophagy exerts anti-apoptosis effects, which promote cell survival. In this research, only male rats were used to reduce the impact of gender differences on research results. However, further experiments need to be validated with female animals.

CONCLUSION

In conclusion, we demonstrated that Baicalin prolongs seizure latency, ameliorates hippocampal injury, increases the survival rate of hippocampal neurons, and reduces mitochondrial apoptosis following SE in rats through autophagy activation. This study contributes to the pharmacological effects of traditional Chinese herbs such as Baicalin. Furthermore, it provides a new way of regulating autophagy for treating SE.

ARTICLE HIGHLIGHTS

Research background

Autophagy is associated with hippocampal injury after status epilepticus (SE), and is considered a potential mechanism with curative value. Baicalin, an emerging multi-therapeutic drug that has been demonstrated to exert neuroprotective effects in patients with nervous system diseases because of its antioxidant property.

Research motivation

We investigate the influence of Baicalin on the improvement of LiCl-Pilocarpine-induced rat SE.

Research objectives

We intended to investigate the potential role of autophagy in LiCl-pilocarpine-induced SE.

Research methods

Nissl staining showed that Baicalin attenuates hippocampal injury and reduces the number of neuronal deaths in the hippocampus. Besides, the expression intensity of cleaved caspase-3 and apoptosis in hippocampal CA1 following SE were reversed by Baicalin, as proven by western blotting and terminal deoxynucleotidyl transferase dUTP nick end labelling assay. Furthermore, western blotting and immunofluorescence staining were used to measure the expression of autophagy markers (p62/SQSTM1, Beclin 1, and LC3) and apoptotic pathway markers (cleaved caspase-3 and Bcl-2).

Research results

Baicalin significantly upregulated autophagic activity and downregulated mitochondrial apoptotic pathway markers. Conversely, 3-methyladenine, a commonly used inhibitor of autophagy, was simultaneously administered to inhibit the autophagy induced by Baicalin, abrogating the latter's protection on the mitochondria apoptotic level.

Research conclusions

We illustrated that Baicalin induced activation of autophagy alleviates apoptotic death and protects the hippocampus of SE rats.

Research perspectives

The improvement of LiCl-Pilocarpine-induced rat SE by Baicalin was validated.

FOOTNOTES

Author contributions: Yang B and Wen HY contributed equally to this work; Yang B and Wen HY proposed the overall research goal and designed the research plan and model design; Yang B, Wen HY, Liang RS, and Lu TM conducted feasibility analysis, review, and supervision of the experiment; Yang B, Wen HY, Zhu ZY, and Wang CH conducted statistical processing and analysis of the data; Yang B and Wen HY are responsible for writing the first draft of the paper; Yang B, Wen HY, and Liang RS were responsible for the review, revision, and quality control of the paper; all authors determined the final draft of the paper.

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ORIGINAL ARTICLE

Basic Study

Exosomal miR-320e through wnt2targeted inhibition of the Wnt/β-catenin pathway allevisate cerebral small vessel disease and cognitive impairment

Zheng Wang, Xue-Ning Li, Shao-Nan Yang, Yuan Wang, Ke-Jin Gao, Bin Han, Ai-Jun Ma

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Abstract

BACKGROUND

Exosomal miRNAs play crucial roles in many central nervous system diseases. Cerebral small vessel disease (CVSD) is a small vessel disease that is affected by various factors. This study aimed to investigate the role of exosomal miR-320e in the Wnt/β-catenin pathway stimulated by oxidative stress and assess its clinical correlation with psychiatric symptoms in patients with CVSD.

AIM

To explore whether exosomal miR-320e could suppress the Wnt/β-catenin pathway and play a protective role in CVSD progression, as well as examine its potential correlation with cognitive impairment and depression in patients with CVSD.

METHODS

Differentially expressed exosomal miRNAs were filtered by sequencing plasma exosomes from patients with CVSD and healthy controls. Bioinformatics and dual luciferase analyses were used to confirm the binding of miR-320e to Wnt2, and the mRNA and protein levels of downstream components in the Wnt/β-catenin pathway were evaluated when overexpressed or with knockdown of miR-320e under H_2O_2-induced oxidative stress. In addition, Wnt2-targeting siRNA was used to confirm the role of miR-320e in the Wnt2-mediated inhibition of the Wnt/β-catenin pathway. A retrospective analysis was conducted among patients with CVSD to confirm the correlation between miR-320e expression and the severity of cognitive impairment and depression, which were quantified using the Montreal

Cognitive Assessment (MoCA)/Executive Function Assessment (EFA), and the Hamilton Depression Scale (HAMD)/Beck Depression Inventory (BDI), respectively.

RESULTS

High-throughput sequencing revealed that exosomal miR-320e was downregulated in patients with CVSD. Bioinformatics analysis and dual-luciferase reporter gene experiments showed that exosomal miR-320e inhibited the Wnt/β-catenin pathway in response to oxidative stress by targeting the 3' noncoding region of Wnt2. Uptake of exosomes carrying miR-320e into endothelial cells could also target Wnt2 and inhibit the Wnt2/β-catenin pathway. Elevated miR-320e expression may protect patients with CVSD from relatively severe cognitive impairment and depression, as it was found to have a positive correlation with the MoCA/EFA and HAMD/BDI scores.

CONCLUSION

Our results suggest that exosomal miR-320e suppresses the Wnt/β-catenin pathway and may play a protective role in CVSD progression.

Key Words: Exosome; Cerebral small vessel disease; miRNA-320e; Wnt2; Wnt/β-catenin pathway; Depressed

Core Tip: Exosomal miR-320e is downregulated in patients with cerebral small vessel disease (CVSD), and it inhibits the Wnt/β-catenin pathway by targeting Wnt2 in response to oxidative stress. Uptake of exosomes carrying miR-320e can also target Wnt2 and inhibit the Wnt2/β-catenin pathway. Elevated miR-320e expression may protect patients with CVSD from severe cognitive impairment and depression, as it correlates positively with Montreal Cognitive Assessment/Executive Function Assessment and Hamilton Depression Scale/Beck Depression Inventory scores. Therefore, exosomal miR-320e may play a protective role in CVSD progression by suppressing the Wnt/β-catenin pathway, indicating its potential as a therapeutic target for CVSD.

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INTRODUCTION

Stroke is the deadliest disease in China and the second most disabling disease worldwide, and its socioeconomic burden has increased dramatically in the last three decades[1]. Cerebral small vessel disease (CVSD) accounts for 20%–30% of ischemic stroke cases. CVSD is a series of clinical, imaging, and pathological syndromes caused by various etiologies that affect the small arteries, microarteries, capillaries, microvenules, and small veins in the brain[2]. White matter and deep gray matter damage caused by CVSD is also considered a major cause of cognitive impairment due to damaged crosstalk between the arteries, capillaries, and small veins[3]. Currently, conventional anti-hypertensive, lipid regulatory, and antiplatelet aggregation treatments are not effective in improving cognitive and motor function impairments in patients [4,5]. Thus, new therapeutic targets or mechanisms for CVSD are warranted.

Exosomes, presenting as 30-150 nm extracellular vesicles in diameter, carry rich contents to exert their bioinformatics function near or distantly[6-8] and have been demonstrated to play important roles in vascular diseases, such as atherosclerosis, diabetic vasculopathy, and stroke[9-11]. Moreover, miRNAs (a class of 17–24 nt small, noncoding RNAs) have been identified in exosomes and are involved in the biogenesis, release, and uptake of relevant proteins by mediating post-transcriptional gene silencing by binding to target mRNAs[12]. Exosomal miRNAs participate in numerous biological processes during nerve injuries. Exosomal miR-451a plays a protective role against cerebral ischemia/reperfusion injury[13]. Exosomal miR-124a can be transported to glioblastomas to play a tumor-suppressive role[14]. Therefore, in this study we performed high-throughput sequencing analysis of plasma exosomal miRNAs between patients with CVSD and healthy controls and found that exosomal miR-320e, with the most significant difference, was speculated to be a highly promising target relevant to CVSD pathogenesis.

With aging and the presence of other risk factors, the integrity of the vasculature is gradually lost. This affects various cellular pathways, including the Wnt/β-catenin pathway, which is known to regulate vascular neogenesis, vascular remodeling, and blood-brain barrier maturation in response to harmful stimuli[15,16]. The Wnt family of proteins has been reported to play essential roles in the development of the nervous system[17]. miRNAs have been found to regulate vascular function by targeting the Wnt pathway, as evidenced by the involvement of miR-29b in vascular smooth muscle calcification[18] and the regulation of miR-330 in the process of unstable atherosclerotic plaque formation and vascular endothelial cell proliferation[19]. These studies indicate that the inhibition of the Wnt/β-catenin pathway may delay the progression of some diseases, such as cancer[20], axonal degeneration[21], and chronic kidney disease[22]. However, the

mechanism by which exosomal miR-320e regulates the Wnt/β-catenin pathway in cerebrovascular disease has not yet been explored.

Among the secretory glycoproteins belonging to the Wnt family, Wnt2 shows potent antidepressant effects and can inhibit the development of depressive disorders, suggesting the direct binding of miR320e to Wnt2[23]. In this study, we assessed the regulatory effects of miRNA-320e on the Wnt/β-catenin pathway by targeting Wnt2 in endothelial cells under oxidative stress. Furthermore, the predictive value of decreased exosomal-derived miR-320e for the clinical deterioration of depression and impaired cognition in CVSD was analyzed in a retrospective study.

MATERIALS AND METHODS

Sequencing of exosomal microRNAs from patients with CVSD

In total, 120 blood samples were collected from patients with CVSD and healthy subjects at the Qingdao University Affiliated Hospital between January 2017 and January 2019 (80 patients with CVSD and 40 controls). Baseline information of the patients with CVSD and controls was shown in the Supplementary Material. The inclusion criteria were based on the STRIVE diagnostic criteria, with the following: (1) Magnetic resonance imaging (MRI) manifestations, including lacunar infarctions, white matter lesions, cerebral microbleeds, and perivascular space enlargement > 2 mm and brain atrophy; (2) Clinical symptoms such as dizziness, fatigue, and cognitive changes; and (3) Age > 18 years. Patients with a definite diagnosis of cardiovascular or cerebrovascular diseases, severe head and neck artery stenosis, arteriosclerosis, incomplete brain MRI, blood system diseases or tumors, or severe liver and kidney insufficiencies were excluded. This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. All specimens were collected after obtaining authorization from the patients and their families and signing a consent form.

Isolation and extraction of exosomes

Thermo Fisher Scientific's Total Exosome Precipitation Reagent (from plasma) kit (REF4484451; Waltham, Massachusetts, United States Thermo Fisher Scientific) was used to extract the exosomes. Although ultracentrifugation was often noted for the ability to produce highly purified exosome, filtration could more conveniently generate a higher yield. However, both filtration and ultracentrifugation methods had their unique advantages and were well accepted in the area of exosome extraction.

The frozen plasma was thawed at room temperature, and 200 μL was placed in an EP tube and centrifuged at 2000 × g for 20 min at room temperature. The supernatant was collected in a new EP tube at room temperature and centrifuged again at 10000 × g for 20 min. Then, 100 μL of Phosphate-buffered saline (PBS) was added to the resulting supernatant and vortexed. Then, 10 microliters of proteinase K (Thermo Fisher Scientific 4485229) was added, shaken well and incubated at 37 °C for 10 min. Then, 60 microliters of extraction reagent was added to the incubated liquid, fully vortexed until turbid, and incubated at 4 °C for 30 min. Next, the sample was removed from the 4 °C environment and centrifuged it at 10000 × g for 5 min at room temperature. A pale yellow or colorless precipitate was observed, and the supernatant was discarded. Finally, we resuspended the sample in 100 μL of PBS to obtain an exosome solution and proceeded to the next step immediately or stored it at -80 °C.

Identification of exosomes

The morphology of the exosomes was observed by transmission electron microscopy, and the quality of the isolated exosomes was determined by nanoparticle tracking analysis. Exosome surface proteins were examined using western blotting.

Extraction of exosomal RNA

Total RNA was extracted using the miRNeasy Serum/Plasma Kit (50) (Cat. No. 217184). Immediately or after thawing the cryopreserved exosome solution, we took 100 microliters for lysis with 500 microliters of TRIzol and incubated at room temperature for 5 min. After addition of 100 μL of chloroform, the sample was vortexed and incubated at room temperature for 3 min. The samples were centrifuged at 12000 × g for 15 min at 4 °C. We transferred the upper part of the aqueous phase after centrifugation into a new EP tube, added absolute ethanol, mixed well, transferred to a spin column, centrifuged at 8000 × g for 15 s, and discarded the filtrate. Then, we added 700 microliters of RWT to the spin column at room temperature, centrifuged at 8000 × g for 15 s, and discarded the filtrate; added 500 microliters of RPE to the spin column at room temperature, centrifuged at 8000xg for 15 s, and discarded the filtrate; added 500 microliters of 80% ethanol, centrifuged the spin column at room temperature at 8000 × g for 2 min, changed the spin column into a new EP tube, and centrifuged at 12000 × g for 5 min for drying. Finally, 14 μL of enzyme-free water was added, and approximately 14 μL of total RNA was obtained by centrifugation at 12000 × g for 1 min after 1 min.

Cell culture

Human umbilical vein endothelial cells (HUVECs), cell models with stem cell potential commonly used for vascular endothelial cell experiments, were cultured in 90% dulbecco's modified eagle medium (DMEM) containing 10% FBS and 1.5% penicillin-streptomycin. All cells were cultured in 5% CO_2 at 37 °C in a humidified atmosphere. DMEM, FBS, and penicillin-streptomycin were purchased from BI (BI, United States), and trypsin was purchased from Thermo Scientific. Oxidative stress stimulation was induced using a 1 mmol/L solution of DEME prepared with hydrogen peroxide for 30 min. R-Spondin-1 (the Wnt pathway agonist) and WIF1 (the Wnt pathway inhibitor) were procured from MCE (MCE,

United States) using complete medium diluted to 60 and 20 ng/mL, respectively, for 24 h of cell culture before subsequent treatment as needed. The plasmids of wild-type and mutated Wnt2 3'-UTR and Wnt2-targeting siRNA, as well as the miR-320e mimic and inhibitor required for the transfection of HUVECs, were constructed by Gikai Gene (Shanghai Genechem Co, Ltd.).

Plasma membrane staining

We used a DiI (DiI perchlorate, C59H97CIN2O4) cell membrane orange-red fluorescent probe to stain the cell and exosome membranes (Yeasen; 40726ES10, China), and absorbance was detected at 550/567 nm.

Western-Blot analysis for protein expression detection

Cell lysis buffer (Elabscience Biotechnology Co., Ltd., China) for western blotting was used for total protein extraction. Following centrifugation at 4 °C (12000 × g, 15 min), a BCA kit (Elabscience, China) was used to quantify the protein concentrations. Protein samples were separated using polyacrylamide gel electrophoresis and transferred onto membranes (ACE Biotechnology, China). Freshly prepared Tris-buffered saline (TBS) containing 5% nonfat milk was used to block the membranes for 2 h at room temperature. The blots were probed with primary antibodies at 4 °C overnight at a dilution ratio of 1:1000. The primary antibodies used for the detection of Wnt/β-catenin pathway by western blotting were as follows: Wnt2, FZD2, Axin2, GSK3β, and β-catenin (Proteintech Group, Inc, United States). Membranes coated with primary antibodies were washed three times with TBS-0.05% Tween 20, followed by incubation at room temperature with the corresponding secondary antibodies for 1 h. The blots were then incubated in the dark with ECL and visualized by exposure to enhanced chemiluminescence reagents (GE Healthcare, United States). ImageJ software 1.4.3.67 (National Institutes of Health, United States) was used to analyze the grey scale values of the blots.

Detection of gene expression with real-time PCR

Total RNA was isolated from the cells using TRIzol Reagent (Invitrogen, United States). Goldenstar RT6 cDNA Synthesis Kit Ver. 2 (TSINGKE, China) was used to synthesize cDNA from the RNA. Wnt2, FZD2, Axin2, GSK3β, and β-catenin were detected by a 2xT5 Fast real-time polymerase chain reaction (PCR) Mix (SYBR Green I) kit (TSINGKE, China). Primer design and synthesis were performed by the Sangon Corporation (Shanghai, China), and the primer sequences were listed in the Supplementary Material. The results of RT-PCR analysis were calculated by the − ΔΔCt method.

Retrospective clinical study in patients with CVSD

Patients and Ethics: Using a retrospective analysis, relevant information on patients with CVSD who met the inclusion criteria was collected between January 2022 and December 2022 at the Department of Neurology of Qingdao University Affiliated Hospital. The inclusion criteria were as follows: (1) Aged–50-80 years; (2) Meeting the diagnostic criteria for CVSD according to the Expert Consensus on Diagnosis and Treatment of CVSD in China (2021); and (3) Agreement to participate in this study and signed an informed consent form. The exclusion criteria were as follows: (1) Other neurological or psychiatric diseases affecting cognitive function; (2) Other systemic diseases or medication history affecting vascular function; and (3) Other factors affecting exosome isolation or detection. Healthy volunteers who underwent physical examinations at the health examination center during the same period were enrolled as controls after obtaining informed consent and met the following conditions: (1) No clinical symptoms or signs; (2) No abnormal laboratory or imaging examinations; and (3) No history of chronic diseases or medication use. This study was approved by the ethics committee of our hospital. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Treatments: Standard therapies were provided to patients with CVSD after a comprehensive assessment of their condition. Doctors developed a personalized treatment plan targeting the risk factors for CSVD in each patient, including anti-hypertensive drugs (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, or β-receptor blockers), antiplatelet drugs (such as aspirin, clopidogrel, or ticagrelor), anticoagulation drugs (such as warfarin, dabigatran etexilate, or rivaroxaban), lipid-lowering therapy (such as simvastatin and atorvastatin), and diabetes controlling drugs (such as insulin and metformin). In addition, lifestyle improvements, such as quitting smoking, limiting alcohol intake, maintaining a healthy diet, and engaging in appropriate exercise, were recommended. For cognitive dysfunction related to CVSD, cholinesterase inhibitors and memantine were chosen to improve depression, anxiety, apathy, and psychiatric symptoms.

Psychiatric Assessments: The following assessment scores of patients were collected: (1) Cognitive function assessment, including the Montreal Cognitive Assessment (MoCA) and the Executive Function Assessment (EFA); and (2) Depression symptom assessment, including the Hamilton Depression Scale (HAMD) and the Beck Depression Inventory (BDI). Utilizing the average scores that patients received as the cutoff point, the CVSD population in this study was divided into two groups: Relatively more severe and relatively better disease.

Statistical analysis

Statistical analysis was performed using SPSS 26.0. Quantitative data were presented as the mean ± SD and were compared using the Wilcoxon test between the two groups, while categorical data were expressed as frequencies (percentages). For western blotting, the mean normalized gray level in the control group was defined as a relative FC of 1. For qRT-PCR, all data were normalized to the FC of the control group. Correlation analysis was performed using the Spearman's rank correlation coefficient. Statistical significance was set at $P < 0.05$. The statistical method of this study was reviewed by Ai-Jun Ma from Qingdao University Affiliated Hospital.

RESULTS

Identification of the miRNA expression profiles in CVSD patients

The results of the identification of the extracted exosomes were shown in Supplementary Material. In total, 120 blood samples were collected from 80 patients with CVSD and 40 healthy controls. The expression of miRNAs in plasma exosomes from patients with CVSD and healthy controls was detected by high-throughput detection. As shown in Figure 1A, the results showed that the expression of 38 miRNAs was significantly different in the plasma exosomes of patients with CVSD compared with the controls. Among these differentially expressed miRNAs, 18 miRNAs were significantly upregulated and 20 miRNAs were downregulated. A heatmap of the miRNAs with significant differential expression was shown in Figure 1B. Next, miR320e, miR-498, miR-6776, and miR-455 were verified using real-time PCR. This trend in the real-time PCR results was consistent with that of the miRNA sequencing results. Previous studies have shown that miR-320 regulates the biological behavior of ischemic neurons and changes the state of tissue inflammation and oxidative stress through drug regulation[24,25]. miR-320e was significantly downregulated compared with that in the healthy control group (16.8478, 95%CI = 7.4456–26.2501), and the difference was statistically significant ($P < 0.001$) (Supplementary Material), indicating that this molecule might play an important role in the pathophysiological process of CVSD.

MiR-320e targets the Wnt2 gene and exerts post-transcriptional regulation

According to the RNACentral and TargetScan human databases, Wnt2 was one of the target mRNAs of miR-320e. In addition, functional enrichment analysis showed that miR-320e was involved in the regulation of cellular responses to stress, mRNA metabolic processes, cell division, and apoptosis (Figure 1C), which was associated with vascular endothelial structural integrity. In contrast to other differentially expressed miRNAs, miR-320e and its target gene Wnt2 were associated with both leukocyte transendothelial function and vascular structural integrity, leading us to speculate that miR-320e may play an important role in the progression of CVSD development.

To verify the binding relationship between miR-320e and Wnt2, we performed a dual-luciferase reporter assay. The plasmids of wild-type and mutated Wnt2 3′-UTR were constructed and cotransfected with overexpressed miR-320e and control mimics. The results showed that the fluorescence intensity in the WT-Wnt2/miR320e-overexpressed group was significantly reduced (Figure 2A and B), indicating that miR320e specifically bound to Wnt2. A two-factor recovery experiment was conducted to prevent off-target effects. The results showed that the protein expression of Wnt2, Axin2, β-catenin, FZD2, and GSK3β was downregulated in the group that was transfected with the miR-320e mimic. In contrast, the endothelial cells transfected with the inhibitors targeting miR-320e showed higher expression of Wnt2, Axin2, β-catenin, FZD and GSK3β than those in the control group (Figure 2C and D). The fluorescence photos observed after transfection of miR-320e mimic and inhibitor were shown in Figure 2E. These results indicated that miR-320e inhibited the expression of Wnt2 at the post-transcriptional level as well as the activation of downstream β-catenin pathways.

The Wnt/β-catenin pathway was involved in the H_2O_2-induced oxidative stress response

HUVECs were treated by adding H_2O_2 to the medium to create oxidative stress in the cell culture environment. The expression levels of Wnt2, FZD2, Axin2, GSK3β and total β-catenin in the Wnt/β-catenin pathway were all increased (Figure 3A-C). Oxidized HUVECs were further stimulated with the Wnt pathway inhibitor WIF1 or the agonist R-spondin in parallel with the mock control. We found that the protein expression of Wnt2, FZD2, Axin2, GSK3β and total β-catenin in the WIF1 + H_2O_2-treated group was similar to that in the WIF1-treated group without oxidative stress, meaning the Wnt2 inhibitor effectively alleviated the H_2O_2-induced Wnt/β-catenin pathway (Figure 3D-G). Meanwhile, R-spondin activated the Wnt2-mediated β-catenin pathway, and the expression of downstream components in the R-spondin + H_2O_2 group was enhanced compared to that in the group treated with R-spondin alone (Figure 3D and F-H). The above data indicate that the Wnt/βcatenin pathway and its relevant components were upregulated under H_2O_2-induced oxidative stress.

miR-320e inhibited the H_2O_2-induced Wnt/β-catenin pathway through targeting Wnt2

To demonstrate the effects of transfection, we used plasmids or siRNAs with green fluorescent labels and puromycin resistance. The fluorescence images observed after transfection of miR-320e mimics, mimic control, Wnt2-targeting siRNA, and siRNA control were shown in Figure 4A and B. Utilizing H_2O_2–treated HUVECs, when signaling in the Wnt/β-catenin pathway including Wnt2 was obviously inhibited by miR-320e mimics compared with control mimics, Wnt2-targeting silencing but not the siRNA control reversed the inhibition of the Wnt/β-catenin pathway (Figure 4C). Protein and mRNA expression detected by western blotting and real-time PCR showed similar results under H_2O_2-induced oxidative stress (Figure 4D-G). These data show that miR-320e inhibited the H_2O_2–induced Wnt/β-catenin pathway by targeting Wnt2.

Exosomes could be taken up by endothelial cells and release their loaded miR-320e into the endothelium to bind to Wnt2 for inhibitory effects

HUVECs were cultured using miR-320e mimics (Figure 5A), and the lipid membranes in the system were stained with DiI, a lipophilic stain with red fluorescence. We collected fresh culture medium and extracted the exosomes secreted by HUVECs to treat another group of HUVECs, and then tested the expression of Wnt2 and β-catenin in the exosome-treated and control groups. The results showed that HUVECs could be stained with DiI (Figure 5B), and we detected the collected exosome suspension in a microplate reader. We observed an increase in the absorbance at 550 and 567 nm

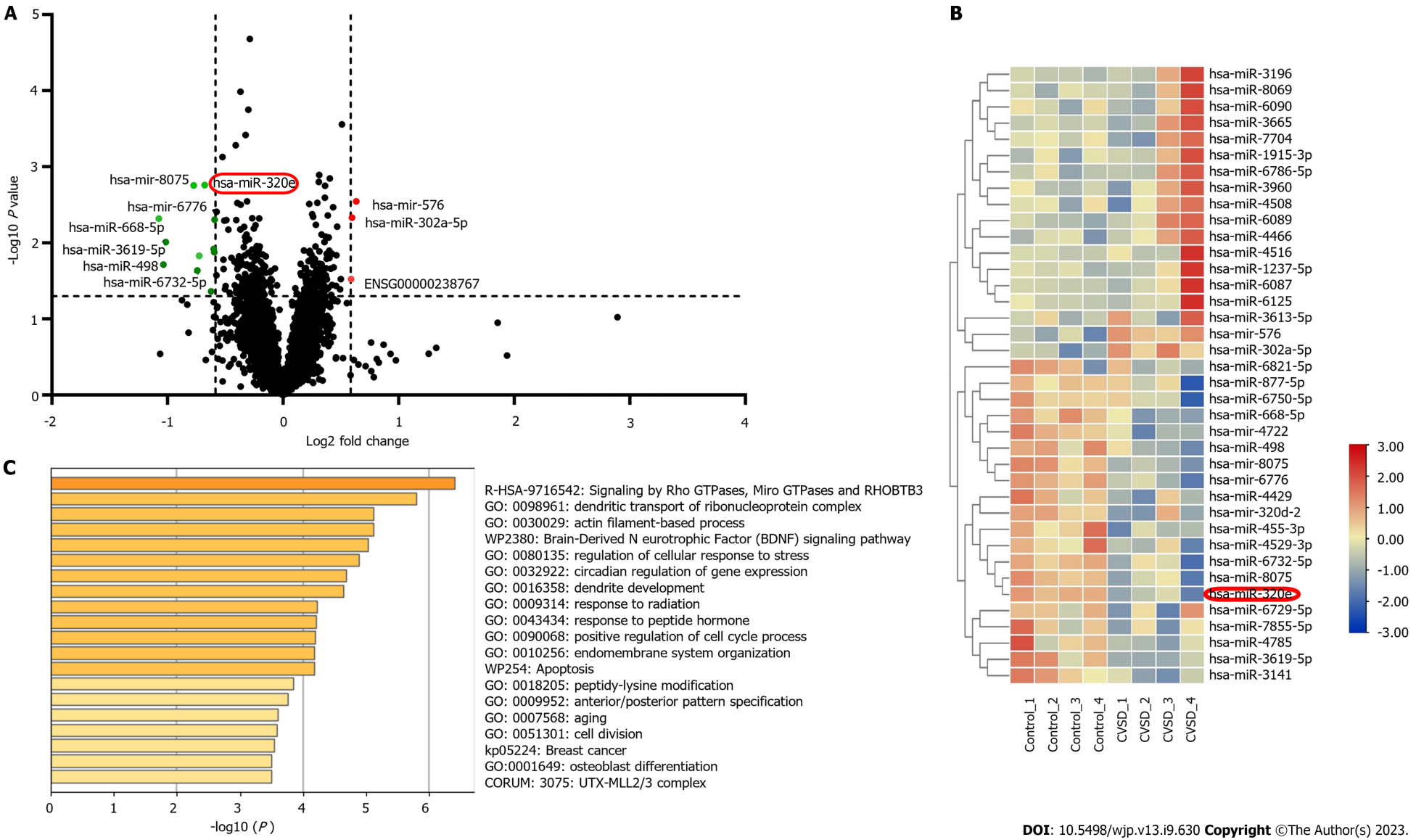

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Figure 1 Construction and bioinformatics analysis of differentially expressed miRNA libraries. A: Volcano diagram showing that miRNA-320e was significantly downregulated; B: High-throughput sequencing of plasma exosomes showed that the expression of miR-320e was significantly downregulated; C: Bioinformatics suggested the biological processes involved in differentially expressed miRNAs. Further information was shown in the Supplementary Material.

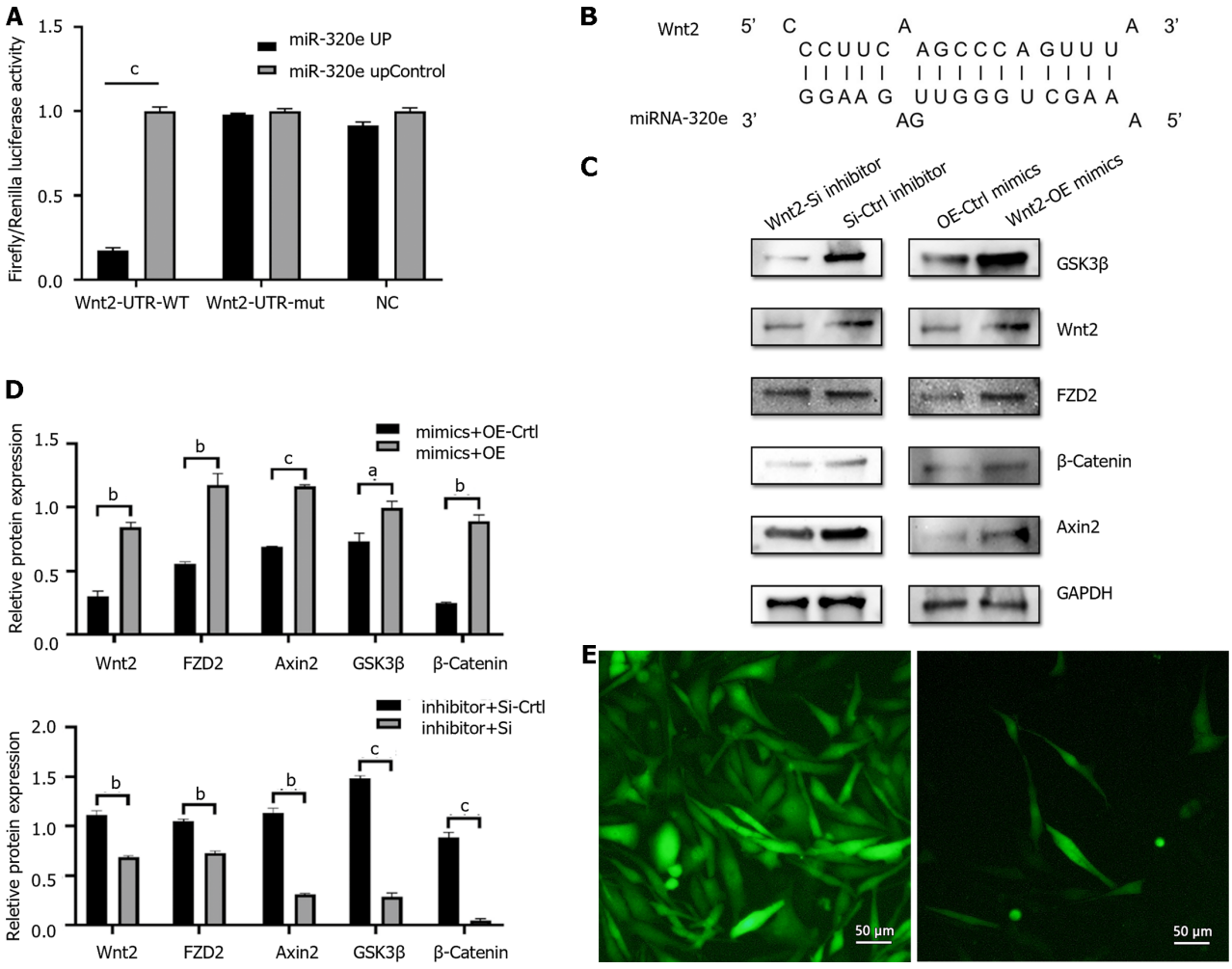

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Figure 2 miR-320e could bind to Wnt2 to inhibit the Wnt/β-catenin pathway. A: The results of the dual-luciferase reporter gene experiment; B: Binding sequence between Wnt2 mRNA and miR-320e; C and D: Protein blots were listed in the column. After cotransfection of the miR-320e mimic, western blotting showed that Wnt2, FZD2, Axin2, GSK3β, and β-catenin expression increased compared with that of the control group. After cotransfection of the miR-320e inhibitor, western blotting showed that Wnt2, FZD2, Axin2, GSK3β, and β-catenin expression decreased compared with that of the control group; E: Cell image after cotransfection of cells. The image above showed transfection with miR-320e mimic and the one below showed transfection with miR-320e inhibitor. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$.

(Figure 5C). Using the collected exosomes secreted by DiI-stained endothelial cells to treat unstained and treated endothelial cells, we observed red fluorescence in the unstained cells after exosome treatment. In addition, we used these exosomes to treat human aortic vascular smooth muscle cells (HASMCs) and observed red fluorescence in these HASMCs (Figure 5D), indicating that HUVEC-derived exosomes could be secreted into the extracellular environment and taken up by other cells. In the Exo/miR-320e-mimic group, Wnt2 mRNA and β-catenin protein and mRNA levels were lower than those in the control group (Figure 5E-G). The above information proves that exosomes can be taken up by other cells, and miR-320e loaded into exosomes enters the cells and exerts an inhibitory effect on Wnt/β-catenin pathway activation by targeting Wnt2.

Retrospective analysis in patients with CVSD

In the same population for exosome extraction, 80 patients with CVSD (42 men and 38 women) with an average age of 66.3 years were included. The average educational level was 9.2 years. Among these patients, 60 patients had hypertension, 24 patients had diabetes, and 36 patients had hyperlipidemia, while the remaining patients did not have respective diseases. Additionally, 28 patients had a history of smoking and 16 patients had a history of alcohol consumption. At the baseline of disease characteristics, 40 patients (50%) had lacunar infarctions, 20 (25%) had cerebral microbleeds, and 20 (25%) had mixed-type CSVD. The white matter hyperintensity burden of the CVSD patient group at enrollment was 12.5 ± 4.2 cm^3, and the total CSVD burden score was 3.2 ± 1.1 points.

The correlation between exosomal miR-320e levels and psychiatric symptoms in patients with CVSD was characterized by Pearson's correlation analysis, which suggested that miR-320e was positively correlated with both cognitive impairmentrelated MoCA/EFA scores and depression-related HAMD/BDI scores (all $P < 0.05$), as shown in Table 1. Based on the scores for cognitive function and depressive symptoms of patients, we found that patients with relatively severe cognitive impairment and depression had statistically lower expression levels of miR-320e in the extracted exosomes than patients in relatively good condition (all *P*-values < 0.05), as shown in Table 2.

Table 1 Correlation analysis of exosomal miR-320e levels with clinical assessment results in cerebral small vessel disease patients

Variable	Spearman correlation coefficient	*P* value
MoCA score	0.328	0.003
EFA score	0.301	0.006
HAMD score	-0.296	0.007
BDI score	-0.283	0.010

MoCA: Montreal Cognitive Assessment; EFA: Executive Function Assessment; HAMD: Hamilton Depression Scale; BDI: Beck Depression Inventory.

Table 2 miRNA levels by groups of more and less severe symptoms of cognitive impairment or depress in cerebral small vessel disease patients, *n* (%)

Assessment Scale	More severe disease (below the average score)		Less severe disease (beyond the average score)		*P* value of miRNA-levels
	Patients	miRNA level	Patients	miRNA level	
MoCA	45 (56.25)	1.18 ± 0.32	35 (43.75)	2.15 ± 0.45	0.010
EFA	40 (50)	1.25 ± 0.40	40 (50)	2.30 ± 0.50	0.0092
HAMD	50 (62.5)	1.10 ± 0.35	30 (37.5)	2.20 ± 0.55	0.030
BDI	38 (47.5)	1.15 ± 0.38	42 (52.5)	2.25 ± 0.48	0.0012

MoCA: Montreal Cognitive Assessment; EFA: Executive Function Assessment; HAMD: Hamilton Depression Scale; BDI: Beck Depression Inventory.

DISCUSSION

The Wnt/β-catenin pathway is involved in the response to oxidative stress stimuli and leads to white matter lesions and central nervous system inflammation and injury[26-28]. Inhibition of the abnormal activation of the Wnt/β-catenin pathway was shown to delay coronary artery disease in the myocardial tissue of rats[29] and the process of renal ischaemia-reperfusion injury involving oxidative stress in the kidney[30]. Inhibition of the Wnt/β-catenin pathway also inhibited the progression of neuroblastoma and attenuated axonal degeneration in Parkinson's disease models[20,21,31]. However, studies on the involvement of the Wnt/β-catenin pathway in CVSD are lacking. Based on the widespreadly applied model of HUVECs in the study of cerebral vasculature, our study showed that miR-320e inhibited the oxidative stress-induced Wnt/β-catenin pathway by targeting Wnt2 in endothelial cells to facilitate a protective role in CVSD. The miR320e expression in patients with CVSD was significantly lower in those with relatively severe cognitive impairment and depression, with a positive correlation with both MoCA/EFA and HAMD/BDI scores. Thus, we speculated that miR-320e could be a potential predictive and therapeutic target for CVSD. However, it was important to note that while HUVECs serve as a useful preliminary model, future investigations employing more directly relevant cell types could potentially further reinforce and expand upon our findings.

Due to the scarcity or absence of smooth muscle content in small arteries, smallvessel diastolic function and substance screening are dependent on endothelial cells to perform normal physiological functions, which are influenced by a combination of factors[32-35]. Recent studies have shown that exosomes transport complex substances that freely reach and cross the blood-brain barrier (BBB), and the miRNAs carried are protected by the exosome membrane from degradation by RNA enzymes so that they can effectively act on target cells. Thus, exosomal miRNAs are considered to affect cerebrovascular disorders by affecting the microenvironment of intracranial vessels[36,37]. Previous studies have found that neuronal-secreted exosomal miR-132 can regulate cerebrovascular integrity[38], exosomal miR-451a may play a protective role in ischemia-reperfusion injury[13], and exosomal miR-124a from mesenchymal stem cells can target and inhibit FOX A2 to suppress glioblastoma[14]. Our study showed that exosomes could carry miR-320e into HUVECs, allowing miR-320e to target Wnt2 to exert inhibition of the Wnt/β-catenin pathway during oxidative stress.

To verify the inhibitory effect of miR-320e on the Wnt/β-catenin pathway, we detected the binding target of Wnt2 and the downstream components of FZD2, Axin2, GSK3β and total cellular β-catenin. Our experiment showed that the oxidative stressinduced enhanced Wnt/β-catenin pathway was significantly inhibited by miR320e, as evidenced by the significant suppression in the above genes. In addition, exosomes carrying miR-320e exerted a similar inhibitory effect on the Wnt/β-catenin pathway. Furthermore, we found that GSK3β was inhibited by miR-320e to a much lesser extent than the other genes in the Wnt/β-catenin pathway. GSK3β is involved in multiple pathways, in addition to its role in the Wnt/β-catenin pathway, representing a class of components that exert pathway interactions during cell signaling[39], which suggests that other miRNAs carried by the experimental exosomes from patients with CVSD may contribute to disease deterioration through other mechanisms.

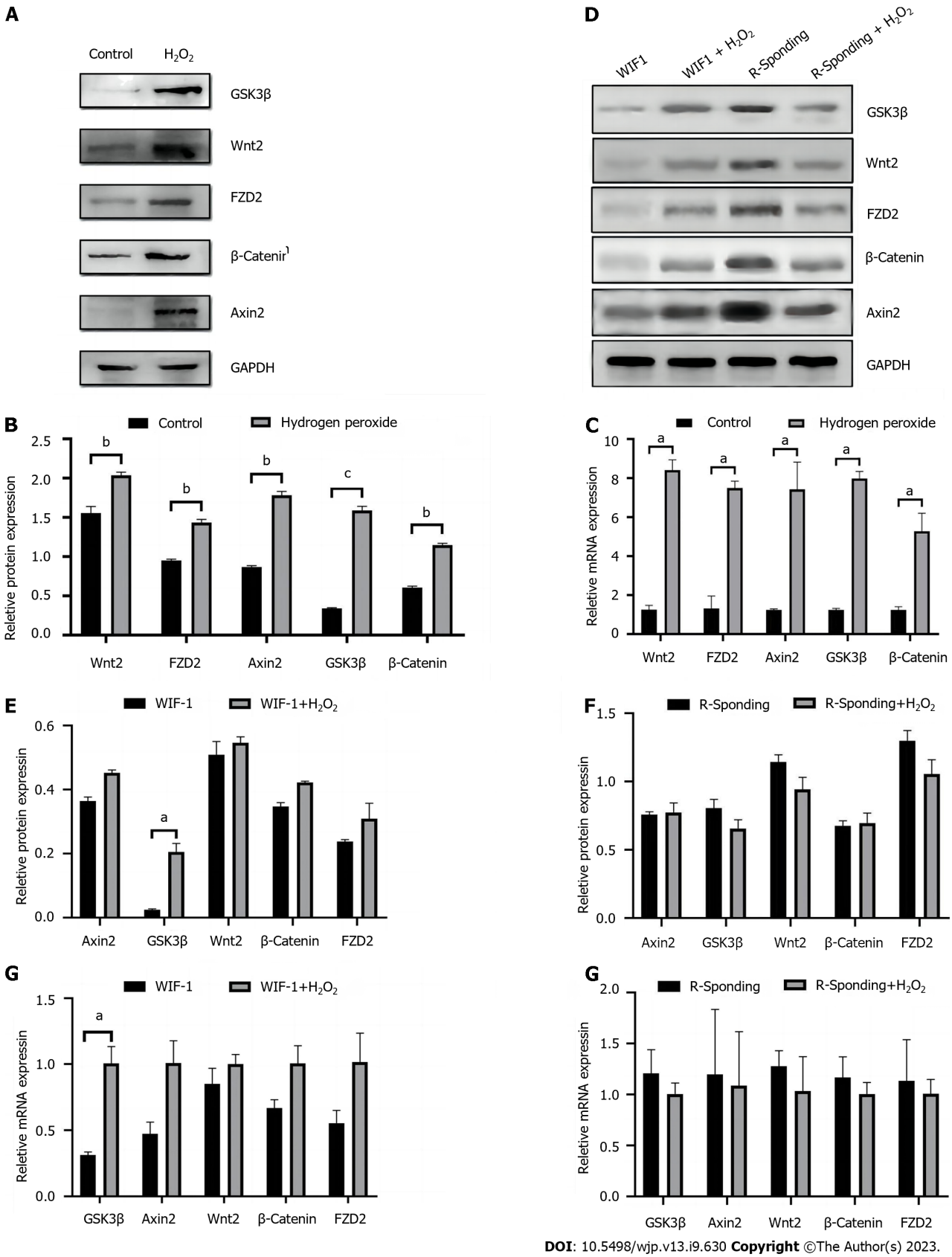

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Figure 3 Representative protein blots of Wnt2, FZD2, Axin2, GSK3β, and β-catenin expression under hydrogen peroxide. A and B: The Western-Blot results showed that Wnt2 expression in the hydrogen peroxide group increased compared to that in the control group; C: The PCR results showed that Wnt2 expression in the hydrogen peroxide group increased compared to that in the control group; D-F: Expression of Wnt2, FZD2, Axin2, GSK3β, and β-catenin expression after treating with WIF1 and R-Spondin under hydrogen peroxide were similar and further enhanced, respectively, compared to that in the groups without hydrogen peroxide; G and H: The PCR results showed that GSK3β in the WIF + H_2O_2 group increased, and the other mRNA expression levels remained similar. PCR: Polymerase chain reaction. $^aP < 0.05$, $^bP < 0.01$, $^cP < 0.001$.

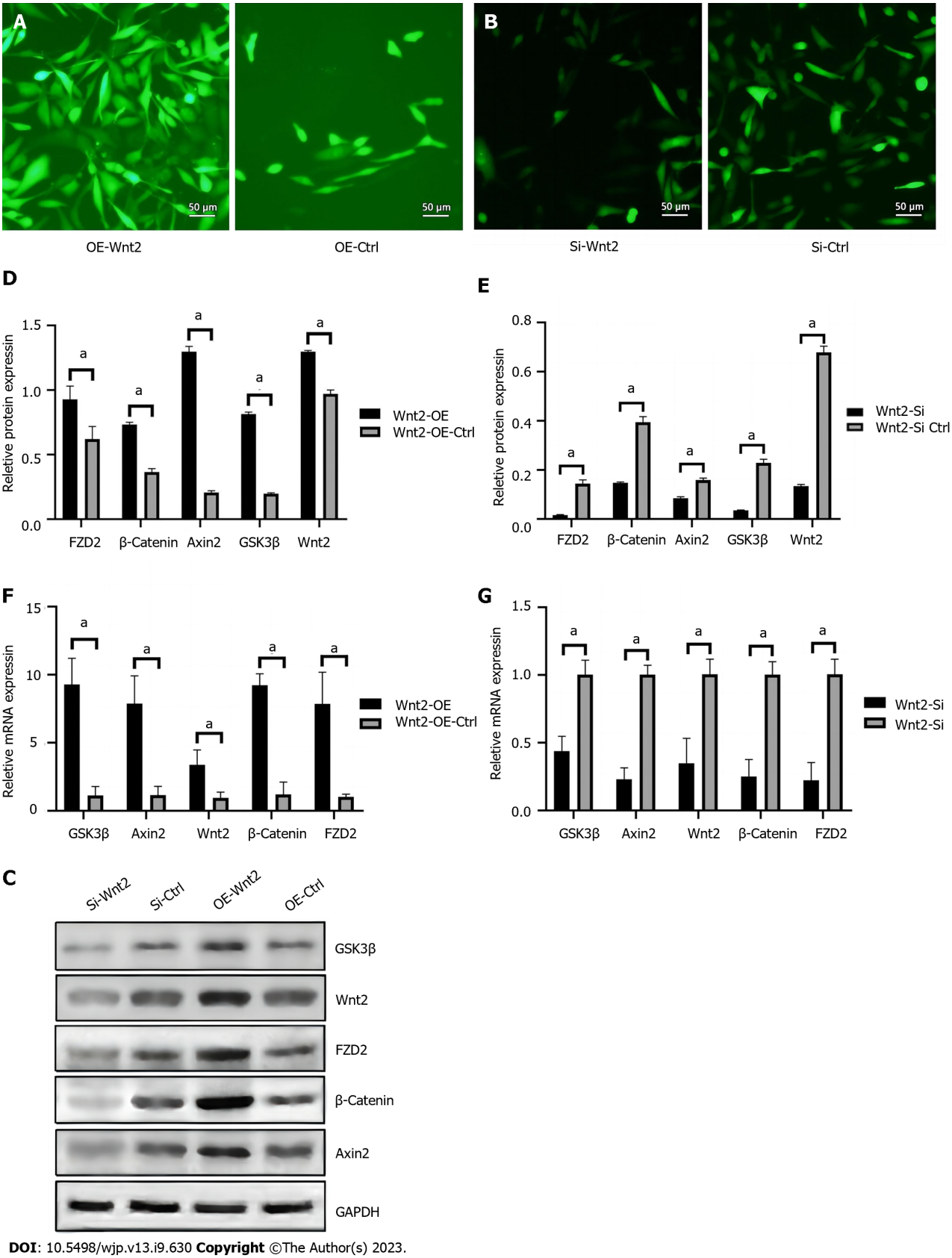

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Figure 4 miR-320e inhibited the Wnt/β-catenin pathway through targeting Wnt2. A and B: Cell transfection images were shown; C-E: The Western-Blot results showed that the expression of Wnt2, FZD2, Axin2, GSK3β, and β-catenin in the miR-320e mimics group was inhibited compared to that in the control group, while this inhibition was effectively blocked by Wnt2 silencing compared to the siRNA control; F and G: The results of real-time PCR showed similar trends to the protein levels of Wnt2, FZD2, Axin2, GSK3β, and β-catenin with overexpressed miR-320e and knockdown of Wnt2. PCR: Polymerase chain reaction. $^{a}P < 0.05$.

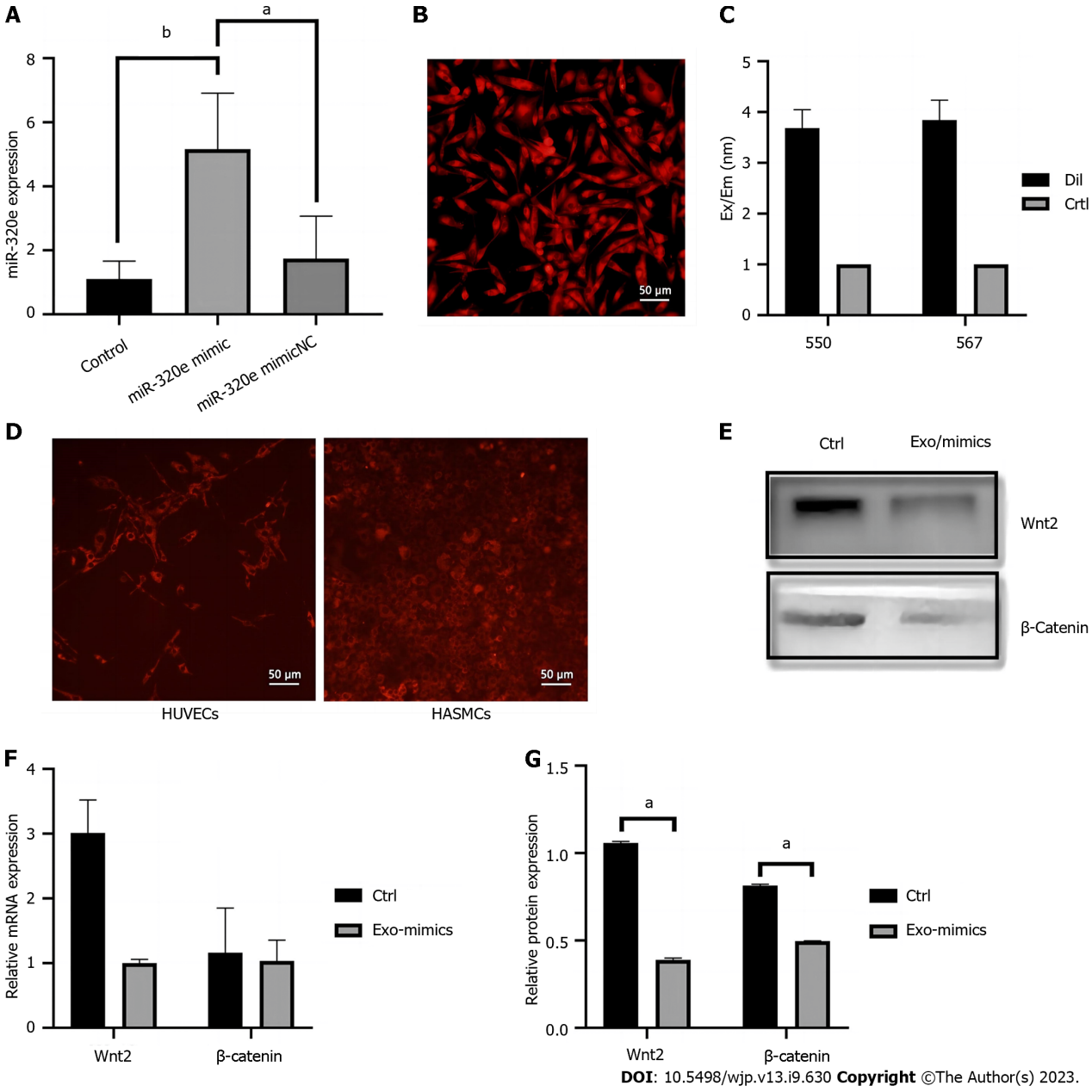

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Figure 5 The expression of miR-320e in the exosomes secreted by the miR-320e mimic-transfected cells was significantly higher than that in the mimic NC group and the blank control. A: HUVECs were transfected using miR-320e mimics and the expression of miR-320e was detected. B: Lipid membrane of HUVECs marked by DiI; C: Microplate reader analysis showed that exosomes were also marked by DiI; D: As shown by using marked exosomes harvested from HUVECs and cocultured with HASMCs, HUVECs also showed red fluorescence; E-G: Western blotting and PCR showed that Wnt2 and β-catenin expression in the Exo-mimic group decreased compared to that of the control group. HUVECs: Human umbilical vein endothelial cells; HASMCs: Human aortic vascular smooth muscle cells; PCR: Polymerase chain reaction. $^{a}P < 0.05$, $^{b}P < 0.01$.

The Wnt pathway has been suggested to exhibit different responses when subjected to different time frames of oxidative stress, with transiently activated Wnt pathways generally inducing neovascularization and protecting vascular structure and cellular function[40,41], and continuously activated Wnt pathways leading to senescence and basement membrane disruption[42]. In CVSD, when the small vessels that develop lesions are not in critical areas of the white matter or cortex or when CVSD is masked by more severe ischemia and hemorrhage, small vessel lesions can be detected at a more advanced stage, while various aggressive factors may allow sustained activation of Wnt/β-catenin, thus promoting CVSD progression. Because of the ability of exosomal miR-320e to target Wnt2 and thereby inhibit abnormal activation of the Wnt/β-catenin pathway, the significantly lower expression of miR-320e in the plasma exosomes of patients with CVSD may lead to a lack of protection. Moreover, other miRNAs with different expression profiles may exert protective effects when combined with miR-320e, which may guide further investigation and validation.

Normal brain function depends on the integrity of the cerebrovascular system, and several underlying pathophysiological mechanisms have been shown to be involved in CSVD, such as BBB damage, small-vessel stiffness, venous collagen proliferation, inflammation, and myelin damage[43,44]. Endothelial cells are the cornerstone of small vessel function; with the natural onset of aging and the onslaught of various risk factors, intracranial vascular function

gradually declines and structural integrity is gradually lost, which has long been seen as a vital process in CSVD[36,45,46]. Currently, there are only a few studies on the mechanisms of action of exosomal miRNAs in CVSD. In summary, using bioinformatics and clinical retrospective analyses, this study predicted and confirmed that the inhibitory role of Wnt2-targeting miR-320e on the Wnt/β-catenin pathway may protect patients with CVSD from relatively severe cognitive impairment and depression, providing a potential novel predictive and therapeutic target for CVSD.

CONCLUSION

Our study demonstrates that exosomal miR-320e plays a significant role in the pathogenesis of CVSD by regulating the Wnt/β-catenin pathway under oxidative stress. Our findings suggest that exosomal miR-320e may be a potential therapeutic target in CVSD based on its ability to inhibit the Wnt/β-catenin pathway and protect against cognitive impairment and depression. The uptake of exosomes carrying miR-320e can also target Wnt2 and suppress the Wnt2/β-catenin pathway, highlighting the significance of exosomal miRNAs as novel therapeutic agents for CVSD. Further studies are needed to investigate the underlying mechanisms of exosomal miR-320e in CVSD progression and to explore its clinical applications. Overall, this study provides new insights into the complex pathophysiology of CVSD and suggests a promising avenue for developing effective therapies for this devastating disease.

ARTICLE HIGHLIGHTS

Research background

Cerebral small vessel disease (CVSD) is a common neurodegenerative disorder characterized by cognitive impairment and depression. Exosomal miRNAs play an essential role in the pathophysiology of CVSD, and their dysregulation contributes to disease progression. This study aimed to investigate the potential role of exosomal miR-320e in the Wnt/β-catenin pathway stimulated by oxidative stress and its clinical correlation with cognitive impairment and depression in patients with CVSD. The study utilized high-throughput sequencing, bioinformatics analysis, dual-luciferase reporter gene experiments, and retrospective analysis among patients with CVSD. The aim was to explore whether exosomal miR-320e could suppress the Wnt/β-catenin pathway and play a protective role in CVSD progression, as well as examine its potential correlation with cognitive impairment and depression in patients with CVSD. The findings suggest that exosomal miR-320e targets Wnt2 and inhibits the Wnt/β-catenin pathway in response to oxidative stress, potentially playing a protective role in CVSD progression. Elevated miR-320e expression may also correlate with less severe cognitive impairment and depression in patients with CVSD.

Research motivation

CVSD is a complex neurodegenerative disorder that affects cognitive function and mental health, but currently lacks effective treatments. Exosomal miRNAs are emerging as important regulators of physiological and pathological processes in the brain, including CVSD. This study aimed to investigate the potential role of exosomal miR-320e in the Wnt/β-catenin pathway stimulated by oxidative stress and its clinical correlation with cognitive impairment and depression in patients with CVSD. The study utilized high-throughput sequencing, bioinformatics analysis, dual-luciferase reporter gene experiments, and retrospective analysis among patients with CVSD. The aim was to explore whether exosomal miR-320e could suppress the Wnt/β-catenin pathway and play a protective role in CVSD progression, as well as examine its potential correlation with cognitive impairment and depression in patients with CVSD. The findings suggest that exosomal miR-320e has a potentially protective role in CVSD progression and may be a novel therapeutic target. The study provides further insights into the complex pathophysiology of CVSD and highlights the importance of exosomal miRNAs in neurological diseases.

Research objectives

The research objectives of this study were to explore the potential role of exosomal miR-320e in the Wnt/β-catenin pathway stimulated by oxidative stress and its clinical correlation with cognitive impairment and depression in patients with cerebral small vessel disease (CVSD). The study aimed to identify differentially expressed exosomal miRNAs by sequencing plasma exosomes from patients with CVSD and healthy controls, confirm the binding of miR-320e to Wnt2 through bioinformatics and dual luciferase analyses, evaluate the mRNA and protein levels of downstream components in the Wnt/β-catenin pathway when overexpressed or knocked down miR-320e under H_2O_2-induced oxidative stress, and conduct a retrospective analysis among patients with CVSD to confirm the relationship between miR-320e expression and the severity of cognitive impairment and depression. The study also aimed to investigate whether exosomal miR-320e could inhibit the Wnt/β-catenin pathway and play a protective role in CVSD progression, potentially leading to the development of novel therapeutic targets for this complex neurodegenerative disorder.

Research methods

The study utilized various methods to investigate the role of exosomal miR-320e in CVSD. Differentially expressed exosomal miRNAs were identified by sequencing plasma exosomes from patients with CVSD and healthy controls. Bioinformatics analysis and dual-luciferase reporter gene experiments were conducted to confirm the binding of miR-

320e to Wnt2. The mRNA and protein levels of downstream components in the Wnt/β-catenin pathway were evaluated through overexpression or knockdown of miR-320e under H_2O_2-induced oxidative stress. Wnt2-targeting siRNA was used to confirm the role of miR-320e in the Wnt2-mediated inhibition of the Wnt/β-catenin pathway. A retrospective analysis was conducted among patients with CVSD to assess the correlation between miR-320e expression and cognitive impairment and depression, which were quantified using the Montreal Cognitive Assessment (MoCA)/Executive Function Assessment (EFA) and the Hamilton Depression Scale (HAMD)/Beck Depression Inventory (BDI), respectively. Overall, these methods provided valuable insights into the potential role of exosomal miR-320e in the pathophysiology of CVSD and its potential clinical significance.

Research results

The results of the study indicate that exosomal miR-320e is downregulated in patients with CVSD. Exosomal miR-320e was found to inhibit the Wnt/β-catenin pathway in response to oxidative stress by targeting the 3' noncoding region of Wnt2. Uptake of exosomes carrying miR-320e could also target Wnt2 and inhibit the Wnt2/β-catenin pathway in endothelial cells. The study also found that elevated miR-320e expression may protect patients with CVSD from relatively severe cognitive impairment and depression, as it had a positive correlation with the MoCA/EFA and HAMD/BDI scores. These findings suggest that exosomal miR-320e may have a potentially protective role in CVSD progression and could be a novel therapeutic target for this complex neurodegenerative disorder. Overall, the results provide important insights into the pathophysiology of CVSD and highlight the importance of exosomal miRNAs in neurological diseases.

Research conclusions

The study found that exosomal miR-320e is downregulated in patients with CVSD and may play a crucial role in the progression of the disease. Exosomal miR-320e was found to inhibit the Wnt/β-catenin pathway by targeting the 3' noncoding region of Wnt2 in response to oxidative stress. The uptake of exosomes carrying miR-320e could also target Wnt2 and inhibit the Wnt2/β-catenin pathway in endothelial cells. Furthermore, elevated miR-320e expression was found to have a positive correlation with cognitive function and depression scores, suggesting it may protect patients from severe cognitive impairment and depression. The study provides new insights into the pathophysiology of CVSD and highlights the potential clinical significance of exosomal miRNAs in neurological diseases. These findings have implications for the development of novel therapeutic targets for CVSD and may provide hope for patients with this complex neurodegenerative disorder.

Research perspectives

The study provides valuable insights into the potential role of exosomal miR-320e in the pathophysiology of CVSD. Future research could investigate the use of exosomal miR-320e as a therapeutic target to prevent or delay the progression of CVSD. Further studies could also investigate the underlying mechanisms by which miR-320e regulates the Wnt/β-catenin pathway and how it affects cognitive function and depression. In addition, the use of animal models could provide further insight into the potential clinical significance of exosomal miRNAs in neurological diseases. Further research could also explore the potential diagnostic and prognostic value of miR-320e in patients with CVSD. Overall, the findings of this study pave the way for future research on the role of exosomal miRNAs in CVSD and other neurodegenerative disorders.

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FOOTNOTES

Author contributions: Wang Z and Li XN concepted the study; Wang Z, Yang SN and Wang Y collected the data; Wang Z, Gao KJ, Han B and Ma AJ contributed to the formal analysis; Wang Z and Ma AJ contributed to the investigation; Wang Z, Li XN and Wang Y contributed to the methodology; Wang Z, Han B, Gao KJ and Ma AJ supervised the study; Yang SN validated the study; Wang Z and Yang SN contributed to the visualization of the study; Wang Z and Han B originally drafted the manuscript; Wang Z, Li XN, Yang SN, Wang Y Gao KJ Han B and Ma AJ reviewed and edited the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Application of traditional Chinese medicine acupoint needle embedding combined with emotional nursing in patients with gynecological malignant tumors

Zhen Ren, Wen Cui, Ya-Ping Li

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Abstract

BACKGROUND

Few relevant literature reports on applying acupoint press-needle embedding combined with emotional nursing in patients with a gynecological malignant tumor.

AIM

To explore the effect of traditional Chinese medicine acupoint needle embedding combined with emotional nursing on chemotherapy-related nausea and vomiting (CINV), cancer-related fatigue (CRF) and psychological state in patients with gynecological malignant tumors.

METHODS

Retrospective analysis of the clinical information of 84 patients with gynecological malignant tumors treated in our hospital from August 2020 to December 2022 Led to the development of an observation group (n = 42) and a control group (n = 42) based on various nursing approaches. Ondansetron hydrochloride injection was administered to the individuals in the control group. However, the observation group received emotional nursing based on the control group and acupoint press-needle embedding of traditional Chinese medicine. Patients in both groups received the chemotherapy regimen of paclitaxel liposome + carbo-platin/cisplatin. For four weeks, both groups intervened. The CINV grade, quality of life, CRF, psychological status and sleep quality scores of the two groups before and

after intervention were compared.

RESULTS

After intervention, the degree of CINV in the observation group was significantly better than that in the control group. After intervention, the scores of each dimension and total score of FLIE scale were significantly higher than those in the control group. After intervention, the scores of each dimension and total score of Piper Fatigue Scale were significantly lower than those in the control group ($P < 0.05$). After intervention, the scores of avoidance and yield dimensions in the observation group were significantly lower than those in the control group, and the scores of confrontation dimension were significantly higher than those in the control group ($P < 0.05$). After intervention, the sleep quality score of the observation group was significantly lower than that of the control group, and the Karnofsky Performance Status scale score was significantly higher than that of the control group ($P < 0.05$).

CONCLUSION

The acupuncture point needle embedding of traditional Chinese medicine combined with emotional nursing can further reduce the incidence of chemotherapy-related nausea and vomiting in patients with gynecological malignant tumors, improve the quality of life and the degree of CRF, alleviate the bad psychological state, adopt a positive way to face the disease and treatment, and improve the quality of sleep and quality of life.

Key Words: Press-needle; Acupoint; Emotional nursing; Gynecologic malignant tumor; Sleep quality; Chemotherapy-induced nausea and vomiting; Cancer-related fatigue; Mental state

Core Tip: Nausea, vomiting and cancer-related fatigue (CRF) are the most common symptoms during chemotherapy in patients with gynecological malignant tumors. If timely and effective nursing intervention is not given, it is easy to affect the quality of life of patients. Acupressure needle has the advantages of simple operation, safety and convenience, while emotional nursing can effectively alleviate the negative emotions of patients with malignant tumors during chemotherapy. The combination of the two can effectively reduce the incidence of nausea and vomiting, improve the quality of life and the degree of CRF in patients with gynecological malignant tumors.

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INTRODUCTION

Cervical, ovarian, and endometrial cancer are the three most prevalent gynecological malignancies, accounting for approximately 18% of all tumors worldwide[1]. The incidence rate has been rising recently, significantly negatively affecting women's physical and emotional health. Chemotherapy, which can efficiently eliminate cancerous cells and increase patients' overall survival times, is currently the preferred clinical treatment technique. However, while treating diseases, chemotherapy can also suppress normal cells, resulting in the suppression of the immune function of patients and negative responses, such as vomiting and nausea, peripheral neurotoxicity, a decrease in hematopoietic stem cell level, *etc*[2], as well as cancer-related fatigue (CRF), thus affecting patients' chemotherapy compliance. Chemotherapy-induced nausea and vomiting (CINV), which can occur in up to 70% of patients with gynecological malignant tumors during chemotherapy, is the most common adverse response. If not prevented and treated promptly and effectively, it can easily lead to eating difficulties in patients and even an imbalance of water, electrolyte, and acid-base balance in severe cases[3]. CRF is a term used to describe severe, continuous, psychological fatigue in physical, emotional, or cognitive aspects unrelated to recent activities caused by a tumor or tumor treatment and interferes with everyday activities. According to incomplete statistics[4], about 57.84% of patients with gynecological malignant tumors will have CRF during chemotherapy, which is easy to increase the pain of patients and affect the quality of sleep and life. Western medicine mainly uses 5-HT3 receptor antagonists, NK-1 receptor blockers, glucocorticoids and other drugs to treat CINV, which can effectively prevent patients from developing CINV. Still, some patients are prone to constipation, headache and other adverse reactions after Western medicine treatment[5].

Traditional Chinese medicine (TCM) has an extensive history of treating gastrointestinal side effects brought on by chemotherapy and offers the benefits of safe use, ease of use, cheap cost, and lack of side effects, *etc.* The external treatment of traditional Chinese medicine has formed a systematic theory and specific methods in developing traditional Chinese medicine for thousands of years, mainly including press-needle embedding, acupoint application, acupuncture, emotional therapy, *etc.* Acupoint press-needle embedding is a type of external treatment of TCM, which can induce continuous weak stimulation at the acupoint by penetrating the needle into the subcutaneous area of a specific acupoint

[6]. It has the advantages of simple operation, safety and convenience. Emotional nursing is a type of TCM nursing technology that consists of the language guidance method, emotion inter-resistance treatment, and emotional desire adjustment. It can easily relieve the negative emotions of cancer patients undergoing chemotherapy[7]. Few relevant literature reports on applying acupoint press-needle embedding combined with emotional nursing in patients with a gynecological malignant tumor. The clinical effectiveness of acupoint press-needle embedding and emotional nursing in individuals with gynecological cancer is examined in this study using a retrospective analysis method.

MATERIALS AND METHODS

Clinical data

A retrospective analysis was done on the clinical data of 84 patients who received chemotherapy for gynecological malignant tumors at our institution between August 2020 and December 2022. (1) Inclusion criteria: Aged 18-80 years old; the patient was diagnosed with a gynecological malignant tumor by postoperative pathological and cytological examination. Patients who needed chemotherapy; Karnofsky Performance Status scale (KPS) score ≥ 70 points; No other antiemetic drugs were taken 48 h before chemotherapy; Complete clinical data; and (2) Exclusion criteria: Patients with liver and kidney insufficiency; Nausea and vomiting caused by intracranial hypertension, vestibular dysfunction and digestive system diseases; Those with contraindications to press-needle; Mental disorders and cognitive disorders; incomplete case data. The 84 patients were grouped into a control group (n = 42) and an observation group (n = 42) using various nursing techniques.

Methods

Liposome + carboplatin/cisplatin. The control group was given an injection of 0.9% sodium chloride (Sichuan Kelun Pharmaceutical Co., Ltd., Approval No. H20056626), a 100 mL injection of ondansetron hydrochloride [Qilu Pharmaceutical Co., Ltd., (No. H10970065)], and 8 mg intravenously 15 min before chemotherapy. Based on the control group, the observation group received acupoint press-needle embedding treatment and emotional nursing. The acupoints of Guanyuan, Dazhui, bilateral Geshu, Zusanli and Shenshu were selected for press-needle treatment, used alcohol to disinfect the patient's skin at the corresponding acupoint, used tweezers to remove the disposable press-needle, quickly attached the press-needle to the acupoint, pressed and smoothed. The operation was performed at the beginning of chemotherapy, the patient was instructed to press intermittently during treatment, the needle could be removed after 2 d, and the press-needle embedding therapy was performed once every 3 d. Emotional nursing: Chinese medical nursing staff carried out emotional nursing, kept the indoor environment in a calm and bright state, and adopted emotional nursing methods such as language guidance method, emotion inter-resistance therapy, emotional transference method, calming mind method, and emotional desire adjustment: (1) Language guidance method: Following the start of chemotherapy, the responsible nurse assessed the patient's mental health and identified the root reasons for their depression, 30 min for each time; (2) Emotion inter-resistance therapy: After chemotherapy, music therapy was used to help patients relieve negative emotions, guided patients to watch skits, cross talk and other programs, and helped patients increase joy to reduce the sadness of patients; and (3) Emotional transference method: Guided patients to find their interests and hobbies, and transfer their attention to chemotherapy through painting, calligraphy, walking and other ways to alleviate bad emotions. The responsible nurse selected 2-3 emotional nursing methods daily and operated once daily. Both groups were treated for 4 wk.

Observation indicators

Between the two groups, comparisons were made of the basic information, CINV grade, quality of life, CRF, coping style, and sleep quality scores: (1) General data questionnaire: including age, education level, primary tumor site, initial chemotherapy, KPS score and other clinical data; (2) CINV grade classification: Grade 0: No nausea or vomiting; Grade I: Nausea but no vomiting; Grade II: Intermittent vomiting with nausea; Grade III: Vomiting Needs Treatment; Grade IV: Excessive vomiting; CINV grades were assigned on the basis of patient's nausea and vomiting[8]; (3) Quality of life (QoL): The QoL of both groups before and after the intervention was evaluated by the Functional Living Index-Emesis (FLIE)[9], which was divided into two dimensions: nausea and vomiting. Each dimension had 9 items, each scoring according to 1 to 7 levels. The higher the score, the smaller the impact of CINV on functional living; (4) CRF: The Chinese version of the Revised Piper Fatigue Scale (PFS-R)[10] was employed to examine the level of fatigue in the two groups before and following the intervention. It consists of 22 questions and is categorized as follows: Behavior, emotion, perception, and cognition; (5) Mental state: The medical coping style scale[11] was applied to determine the coping style of both groups before and after the intervention, which was divided into three dimensions: Avoidance, yield and facing, with 20 items. The higher the score of each dimension, the more likely the patient was to adopt the coping style; and (6) Sleep quality: The Pittsburgh Sleep Quality Index (PSQI)[12] was utilized to examine 18 items, including seven aspects of sleep latency, sleep duration, sleep efficiency, sleep disorders, hypnotic drugs, and daily dysfunction. The scale ranged from 0 to 21, and the overall score was the average for each item. A total score of ≤ 7 suggested normal sleep quality and sleep disorders by a total score of ≥ 8. The lower the patient's sleep quality, the higher the overall score.

Data collection

Nursing staff who had been trained in a unified manner distributed the general information questionnaire and scales of quality of life, CRF, coping style, and sleep quality to the patients, explained the purpose of this study and the

precautions for filling in the patients before filling in, and checked whether the questionnaire and scale were missing after filling in to ensure the integrity of the questionnaire and scale.

Statistical analysis

In this study, EpiData 3.0 software was used to input data by two people. The data obtained were analyzed and processed with SPSS25.0 software. The counting data is presented as "n (%)", and the comparison was made using the chi-square test. The measurement data following the normal distribution were presented as mean ± SD, and the t-test was employed for comparison. A P value < 0.05 was deemed as statistically significant for all analyses.

RESULTS

General data comparison between the two groups

Table 1 demonstrates no statistically considerable variation in the basic data of both groups (P > 0.05).

The CINV score comparison in both groups following treatment

Following the intervention, the observation group's CINV grade was considerably higher as compared to the control group (P < 0.05; Table 2).

Comparison of pre-and post-intervention QoL values in both groups

The scores for each dimension and the FLIE scale's overall score before intervention did not significantly vary (P > 0.05) in both groups. With statistical significance (P < 0.05), the scores for each component and the overall FLIE scale score in the two groups were higher after the intervention. Following the intervention, the observation group's scores on each component and overall FLIE scale score were significantly higher than those of the control group (P < 0.05; Table 3).

Comparison of CRF scores before and after intervention for both groups

Before the intervention, there was no statistically significant difference (P > 0.05) between the scores of each dimension and the total score on the PFS-R scale in both groups. After the intervention, the scores of each dimension and the total score of the PFS-R scale in the observation group were considerably lower than before the intervention (P < 0.05). In contrast, the scores of each dimension and the total score of the PFS-R scale of the control group pre- and post-the intervention did not demonstrate statistical significance (P > 0.05). Table 4 shows that after the intervention, the score of each dimension and the overall score of the PFS-R scale in the observation group were significantly lower compared to the control group (P < 0.05).

Comparison of coping style ratings before and after intervention in both groups

Before the intervention, no significant difference (P > 0.05) in the scores of medical coping strategies in both groups was observed. Both groups' avoidance and yield dimensions dropped after the intervention compared to before. The scores on the facing dimension improved (P < 0.05) compared to those before the intervention. Following the intervention, the observation group's scores for the avoidance and yield dimensions were significantly lower than those of the control group. The face dimension score was significantly higher compared to the control group (P < 0.05; Table 5).

Evaluation of both groups' KPS scores and sleep quality pre- and post-intervention

Both groups had no significant change (P > 0.05) before the intervention in sleep quality or KPS score. Both groups' sleep quality and KPS scores dropped significantly (P < 0.05) after the intervention compared to before. As shown in Table 6, the observation group's sleep quality score was considerably lower than the control group's after the intervention, while the control group's KPS score was significantly higher (P < 0.05).

DISCUSSION

Epidemiological research shows that[13] the number of patients diagnosed with gynecological malignancies and the number of deaths from such diseases are increasing yearly and have obvious characteristics such as low age and high malignancy, which seriously affect the physical and social psychological health of contemporary women. There are many treatments for gynecological malignant tumors. Adjuvant chemotherapy is an important measure to improve the postoperative survival rate. Since vomiting and nausea are frequent side effects of chemotherapy, therapeutic attention has turned to preventing and treating CINV. Previous clinical studies have suggested that the vomiting mechanism is complex, mainly because the neurotransmitter receptors on the gastrointestinal pheochromocytoma combine with chemotherapy drugs to stimulate the brain centre and send signals to the organs and tissues of the upper digestive tract to complete the vomiting reflex. Among them, important neurotransmitters such as 5-HT and substance P participate in the reaction and bind to the 5-HT_3 receptor and NK-1 receptor, respectively[14].

Therefore, Western medicine often uses 5-HT3 receptor antagonists and NK-1 receptor blockers to prevent nausea and vomiting[15], but long-term use is prone to adverse reactions. Compared with traditional acupuncture, the diameter of the press needle is generally about 0.20 mm, and the length of the needle body varies from 0.30 to 5.00 mm. After the

Table 1 shows the comparisons of demographic data between the two groups, *n* (%)

Item		Observation group (*n* = 42)	Control group (*n* = 42)	t/χ^2 value	*P* value
Age (yr, mean ± SD)		52.49 ± 7.65	52.18 ± 7.83	0.184	0.855
Primary tumor site	Ovarian cancer	14 (33.33)	15 (35.71)	0.236	0.889
	Endometrial carcinoma	3 (7.14)	2 (4.76)		
	Cervical cancer	25 (59.52)	25 (59.52)		
Primary chemotherapy	Yes	18 (42.86)	17 (40.48)	0.049	0.221
	No	24 (57.14)	25 (59.52)		
KPS score (points, mean ± SD)		82.56 ± 5.69	82.33 ± 5.87	0.182	0.856

KPS: Karnofsky Performance Status scale.

Table 2 Comparison of chemotherapy-related nausea and vomiting grade between the two groups after intervention, *n* (%)

Group	*n*	Grade 0	Grade I	Grade II	Grade III	Grade IV
Observation group	42	29 (69.05)	10 (23.81)	2 (4.76)	1 (2.38)	0 (0.00)
Control group	42	15 (35.71)	13 (30.95)	8 (19.05)	5 (11.90)	1 (2.38)
χ^2 value		12.114				
P value		0.017				

Table 3 Compares both group's quality of life scores before and after the intervention

Group	*n*	Nausea dimension		Vomiting dimension		Total score	
		Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Observation group	42	32.30 ± 6.54	40.23 ± 4.52[a]	32.77 ± 6.81	39.87 ± 5.36[a]	63.54 ± 7.81	80.15 ± 6.52[a]
Control group	42	32.08 ± 3.77	33.89 ± 3.59[a]	32.59 ± 6.94	33.72 ± 5.47[a]	63.37 ± 7.95	74.58 ± 7.16[a]
t value		0.189	7.118	0.120	5.204	0.099	3.728
P value		0.851	0.000	0.905	0.000	0.921	0.000

[a]$P < 0.05$.

Table 4 Comparison of cancer-related fatigue scores between both groups before and after intervention (points mean ± SD)

Group	*n*	Behavior		Emotion		Perception		Cognition		Total score	
		Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	After intervention
Observation group	42	3.84 ± 0.57	3.12 ± 0.84[1]	3.91 ± 0.62	2.74 ± 0.36[1]	3.74 ± 0.55	2.78 ± 0.67[1]	3.91 ± 0.32	2.68 ± 0.36[1]	4.11 ± 0.36	2.33 ± 0.41[1]
Control group	42	3.67 ± 0.69	4.64 ± 0.97	3.85 ± 0.72	3.94 ± 0.47	3.66 ± 0.63	3.82 ± 0.54	3.88 ± 0.49	3.97 ± 0.52	3.94 ± 0.48	3.99 ± 0.56
t value		1.231	7.677	0.409	13.136	0.62	7.832	0.332	13.219	1.836	15.5
P value		0.222	0	0.683	0	0.536	0	0.741	0	0.07	0

[1]Indicates significant value.

Table 5 Comparison of coping style scores between the two groups before and after intervention (points mean ± SD)

Group	*n*	Avoidance		Yield		Facing	
		Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Observation group	42	18.56 ± 1.25	11.21 ± 1.08[a]	17.54 ± 1.37	10.23 ± 1.55[a]	11.27 ± 1.58	19.52 ± 1.13[a]
Control group	42	18.41 ± 1.38	13.64 ± 2.55[a]	17.28 ± 1.49	12.19 ± 1.12[a]	11.09 ± 1.67	14.16 ± 1.29[a]
t value		0.522	5.687	0.832	6.642	0.507	20.255
P value		0.603	0.000	0.408	0.000	0.613	0.000

[a]$P < 0.05$.

Table 6 Comparison of sleep quality and Karnofsky Performance Status scale score between the two groups before and after intervention (points mean ± SD)

Group	*n*	PSQI scale		KPS score	
		Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Observation group	42	12.24 ± 2.57	6.54 ± 1.57[a]	82.56 ± 5.69	79.85 ± 6.62[a]
Control group	42	11.97 ± 2.98	9.51 ± 1.68[a]	82.33 ± 5.87	75.71 ± 7.52[a]
t value		0.445	8.371	0.182	2.678
P value		0.658	0.000	0.856	0.009

[a]$P < 0.05$.
PSQI: Pittsburgh Sleep Quality Index; KPS: Karnofsky Performance Status.

needle is inserted into the human body, there is almost no sense of acupuncture. After the needle is applied, it is buried in the body with glue and can be retained for a long time. It has the advantages of simple operation and low price. Traditional Chinese medicine acupoint press needles can achieve a sustained therapeutic effect by continuously stimulating the body and then prolonging the effect of acupuncture[15]. Previous studies have found that[16] applying an acupoint press needle in patients with dermatitis helps promote the blood circulation of patients and has a good analgesic effect. Emotional nursing affects patients' emotions through the words and behaviors of medical staff, thus improving patients' negative emotions, eliminating patients' worries and anxieties, and improving patients' anti-cancer concepts.

This study applied acupoint press needle and emotional nursing to gynecological malignant tumor patients receiving chemotherapy. The results showed that the observation group's post-intervention FLIE scale scores on each dimension and overall were considerably higher compared to the control group and that the observation group's post-intervention CINV grade was higher than that of the control group. The findings indicated that emotional nursing and acupoint press-needle embedding could further lower the prevalence of CINV in patients with gynecological malignant tumors and lessen the negative effects of nausea and vomiting on quality of life. CRF is a subjective feeling often associated with cancer patients. Unlike other common symptoms, CRF does not have obvious physiological changes or measurable physiological indicators[17].

Meanwhile, Chinese women are more tolerant and often hide their fatigue performance to avoid burdening their families, mistakenly believing that fatigue is only temporary. However, studies have shown[18] that persistent CRF leads to a higher risk of death. The findings of this research demonstrated that after the intervention, the observation group's PFS-R scale scores on each dimension and overall were lower than the control group. The statistical significance of the difference suggests that acupoint press-needle embedding combined with emotional caregiving can help reduce the severity of CRF in patients with gynecological cancerous tumors. The study's findings also revealed that the observation group's avoidance and yield dimension scores were significantly lower after the intervention than those of the control group.

Compared to the control group, their face dimension scores were significantly higher, their sleep quality scores were significantly lower, and their KPS scores were higher, indicating that the acupoint press-needle embedding combined therapy had an effect. The acupoint press-needle embedding may produce constant stimulation on particular acupoints, which can have the effect of antiemesis and lessen the negative effects of CINV on quality of life. With emotional nursing measures, the language guidance method, emotion inter-resistance therapy, emotional transference method, calming mind method and other methods were used to relieve the bad mood of patients. Music therapy was used to improve the cerebral cortex excitability to regulate the human body's mood, thus eliminating the tension, anxiety and other feelings of the human body, improving fatigue degree and sleep quality, and establishing confidence in treating disease.

CONCLUSION

In conclusion, Chinese medicine acupoint needle embedding combined with emotional nursing can further reduce the incidence of chemotherapy-related nausea and vomiting in patients with gynecological malignant tumors, improve the quality of life and the degree of CRF, alleviate the bad psychological state, and adopt a positive way to face the disease and treatment, improve sleep quality and quality of life, which is worthy of clinical application.

ARTICLE HIGHLIGHTS

Research background

The number of patients diagnosed with gynecological malignant tumors and the number of deaths from such diseases are increasing year by year. At the same time, it has obvious characteristics such as low age and high malignancy, which seriously affects the physical and social mental health of contemporary women. Nausea and vomiting are common adverse reactions after chemotherapy. Therefore, preventing and improving chemotherapy-related nausea and vomiting has become a hot topic in clinical research. In the past, 5-HT3 receptor antagonists, NK-1 receptor blockers and other drugs were used to prevent nausea and vomiting, but long-term use was prone to adverse reactions. The use of traditional Chinese medicine nursing measures has the advantages of simple operation and good safety.

Research motivation

To observe the application value of traditional Chinese medicine acupoint needle embedding combined with emotional nursing in improving the adverse reactions of gynecological malignant tumor chemotherapy, which can effectively reduce the incidence of nausea and vomiting and cancer-related fatigue (CRF) caused by chemotherapy, improve the treatment confidence and improve the prognosis of patients.

Research objectives

By observing the effect of traditional Chinese medicine acupoint needle embedding combined with emotional nursing on chemotherapy-related nausea and vomiting, CRF and psychological state in patients with gynecological malignant tumors, it is helpful to reduce the incidence of chemotherapy-related nausea and vomiting in patients with gynecological malignant tumors, improve the quality of life and the degree of CRF, alleviate the bad psychological state, adopt a positive and positive way to face the disease and treatment, and improve the quality of sleep and quality of life.

Research methods

By observing the effect of traditional Chinese medicine acupoint needle embedding combined with emotional nursing on chemotherapy-related nausea and vomiting, CRF and psychological state in patients with gynecological malignant tumors, it is helpful to reduce the incidence of chemotherapy-related nausea and vomiting in patients with gynecological malignant tumors, improve the quality of life and the degree of CRF, alleviate the bad psychological state, adopt a positive and positive way to face the disease and treatment, and improve the quality of sleep and quality of life.

Research results

By observing the application value of traditional Chinese medicine acupoint needle embedding combined with emotional nursing in patients with gynecological malignant tumors, it was found that acupoint needle embedding combined with emotional nursing had significant effects on reducing the incidence of adverse reactions to chemotherapy, improving CRF and quality of life of patients. The effect of this program on the long-term prognosis of patients with gynecological tumors still needs to be further verified.

Research conclusions

Traditional Chinese medicine nursing program is of great significance to reduce the incidence of adverse reactions of chemotherapy in patients with gynecological malignant tumors and improve their quality of life.

Research perspectives

In the future, it is necessary to further observe the effect of traditional Chinese medicine nursing technology on improving the long-term prognosis of patients with gynecological malignant tumors.

FOOTNOTES

Author contributions: Ren Z initiated the project and designed the experiment; Cui W conducted clinical data collection; Li YP performed postoperative follow-up and recorded data; Ren Z conducted a number of collation and statistical analysis; Cui W wrote the original manuscript; Li YP revised the paper; all authors reviewed and approved the paper, and read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of factors related to postpartum depression in pregnancy-induced hypertension syndrome patients and construction and evaluation of nomograms

Jie-Wei Pan, Gang Zhao

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Abstract

BACKGROUND

It is positive to integrate and evaluate the risk factors for postpartum depression in patients with pregnancy-induced hypertension syndrome and to detect high-risk patients as early as possible, which has application value for the clinical development of personalized prevention programs and prognosis of patients.

AIM

To analyze factors related to postpartum depression in patients with pregnancy-induced hypertension and construct and evaluate a nomogram model.

METHODS

The clinical data of 276 patients with pregnancy-induced hypertension admitted to Huzhou Maternity and Child Health Care Hospital between January 2017 and April 2022 were retrospectively analyzed. We evaluated the depression incidence at 6 wk postpartum. The depression group included patients with postpartum depression, and the remainder were in the non-depression group. Multivariate logistic regression analysis and the LASSO regression model were applied to analyze the factors related to postpartum depression in patients with pregnancy-induced hypertension. After that, a risk prediction model nomogram was constructed and evaluated.

RESULTS

Multivariate logistic regression analysis showed that vitamin A deficiency (VAD) during pregnancy and puerperium, family history of hypertension, maternal intestinal flora imbalance, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) were independent risk factors for postpartum depression in patients with pregnancy-induced hypertension ($P < 0.05$). We constructed the nomogram model based on these five risk factors. The area under the curve, specificity, and

sensitivity of the model in predicting postpartum depression in patients with pregnancy-induced hypertension was 0.867 (95% confidence interval: 0.828–0.935), 0.676, and 0.889, respectively. The average absolute error was 0.037 (Hosmer-Lemeshow test χ^2 = 10.739, P = 0.217).

CONCLUSION
VAD during pregnancy and puerperium, family history of hypertension, maternal intestinal flora imbalance, EPA, and DHA affect postpartum depression in patients with pregnancy-induced hypertension.

Key Words: Pregnancy-induced hypertension syndrome; Postpartum depression; Unhealthy emotions; Related factors; Nomograms; Evaluation

Core Tip: Pregnancy-induced hypertension usually manifests as an elevation of blood pressure, oedema, multiple organ damage, eclampsia, and even coma. Here, we analyzed the factors related to postpartum depression in patients with pregnancy-induced hypertension. We used vitamin A deficiency during pregnancy and puerperium, family history of hypertension, maternal intestinal flora imbalance, eicosapentaenoic acid, and docosahexaenoic acid to construct a nomogram evaluated and confirmed to have good predictive performance. It is a breakthrough in the prediction of postpartum depression in pregnancy-induced hypertension.

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INTRODUCTION

Pregnancy-induced hypertension is a syndrome caused by elevated blood pressure, with a prevalence of 12%[1]. Elevation of blood pressure, oedema, multiple organ damage, eclampsia, and even coma are common clinical symptoms in patients with pregnancy-induced hypertension, which can increase the risk of maternal and perinatal death. Postpartum depression includes negative emotions such as pessimism, anxiety, loss, and ease of fright after childbirth. In severe cases, there may be suicidal tendencies and dangerous events such as harming infants or others[2]. The incidence of postpartum depression in patients with pregnancy-induced hypertension is about 9.4%, significantly higher than in non-depressed pregnant women[3]. Women can have both hypertension and depression during pregnancy and puerperium, which are a threat to maternal and infant health. The pathogenesis of postpartum depression is still unknown, and it may be related to genetic, mental, biochemical, social, and other factors. Therefore, it is practical to integrate and evaluate the risk factors for postpartum depression in patients with pregnancy-induced hypertension and to detect high-risk patients as early as possible, which is of guiding effects for the clinical development of personalized prevention programs and prognosis of patients. In this study, by analyzing the risk factors for postpartum depression in patients with pregnancy-induced hypertension, we constructed a personalized nomogram model to provide reference data for reducing the occurrence of clinical postpartum depression.

MATERIALS AND METHODS

Patient data

We conducted a retrospective study on 276 patients with pregnancy-induced hypertension in Huzhou Maternity and Child Health Care Hospital between January 2017 and April 2022. The enrolled patients met the following criteria: Diagnosis of pregnancy-induced hypertension[4]; age ≥ 18 years; and complete clinical data, laboratory examination data, and 5-HT1A receptor gene C (-1019)G [5-HTR1AC(-1019)G] detection data. The exclusion criteria were: Abnormal cognitive function; malignant tumours, myocardial infarction, stroke, or other serious diseases; inability to communicate smoothly with language; or prenatal history of mental illness or family history.

Clinical data collection

We collected the clinical data by consulting the electronic medical records of patients, including gestational weeks of pregnancy-induced hypertension, adverse delivery outcomes, adverse delivery history, family support status, vitamin A deficiency (VAD) during pregnancy and puerperium, complications, family history of hypertension, delivery mode, delivery times, education level, planned pregnancy, occupational status during pregnancy and puerperium, feeding mode, 5-HTR1AC(-1019)G, intestinal flora imbalance during pregnancy and puerperium, weight gain during late

pregnancy, age, family monthly income during pregnancy and puerperium, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), hypersensitive C-reactive protein (Hs-CRP), and procalcitonin (PCT).

Definition and detection methods of related indicators

Adverse birth outcomes included premature birth (gestational age < 37 wk), birth defects, low weight, asphyxia, and infection. The family member support score was measured using the social support rating scale developed by Xiao Shuiyuan to evaluate the support of family members (parents, spouses, compatriots, children, and one other). The total score was 4–16 points, divided into four levels: Full strength, general, very little, and no support. The higher the score, the higher the level of family support[5]. In smears of faecal samples taken from patients during pregnancy and puerperium, a large number of suppressed proto-flora, a decrease in the total number of bacteria, an increase in Gram-negative bacteria, or a decrease/increase in Gram-positive bacteria indicated intestinal flora imbalance.

Weight gain in the third trimester was weight in the third trimester minus the initial weight. The boundaries for the classification of pregnant women with normal and overweight initial weight were an insufficient increase, < 11.5 and < 7 kg; sufficient increase, 11.5-16 and 7-11.5 kg; and excess increase, > 16 and > 11.5 kg[6]. At 16 wk of gestation and 6 wk after delivery, the venous peripheral blood serum VA content was determined by HPLC. Serum VA concentration < 0.7 μmol/L was determined as VAD[7]. Complications included thyroid disease, kidney disease, heart disease, and diabetes. The concentration of EPA, DHA, and AA in venous blood serum was determined by the double antibody sandwich method on day 3 after delivery. Hs-CRP and PCT were measured by Roche Cobas 8000C701 biochemical analyzer and Roche E411 Luminescence analyzer, respectively.

Grouping

At 6 wk postpartum, the Edinburgh Postpartum Depression Scale (EPDS)[8] was used to assess depression status. The total score was 0-30 points. The higher the score, the more serious the depression. Patients with EPDS scores ≥ 13 were diagnosed with postpartum depression. Women who met the criteria for postpartum depression fell into the depression group, and the remainder into the non-depression group.

Statistical methods

We analyzed and processed the data using R version 4.0.3 and performed LASSO regression analysis with the glmnet package. We used the rms package to draw the nomogram and calibration curve and the predictive receiver operating characteristic curve (ROC) package to draw the ROC. We verified the resulting nomogram model by bootstrap self-sampling 500 times and evaluated its efficacy by the area under the ROC curve (AUC). The test level was $\alpha = 0.05$.

RESULTS

Comparison of clinical data of patients

Among the 276 patients with pregnancy-induced hypertension, 54 were in the depression group and 222 in the non-depression group. The incidence of postpartum depression in patients with pregnancy-induced hypertension was 19.57% (54/276). We compared the number of gestational weeks, adverse delivery outcomes, family support status, VAD during pregnancy and puerperium, complications, family history of hypertension, maternal intestinal flora imbalance, weight gain in the third trimester, EPA and DHA between the two groups (Table 1).

Multivariate analysis of postpartum depression in pregnancy-induced hypertension

We put independent variables ($P < 0.05$) and dependent variables (grouping, 0 = non-depression group, 1 = depression group) into a multivariate logistic regression analysis model (Table 2). VAD during pregnancy and puerperium, family history of hypertension, intestinal flora imbalance during pregnancy and puerperium, EPA, and DHA were independent risk factors for postpartum depression ($P < 0.05$) (Table 3). The AUC of VAD during pregnancy and puerperium, family history of hypertension, intestinal flora imbalance during pregnancy and puerperium, EPA, and DHA in predicting postpartum depression in patients with pregnancy-induced hypertension were 0.612, 0.584, 0.603, 0.293, and 0.281, respectively. The best cut-off values of EPA and DHA were 1.82 pg/mL and 2.18 pg/mL, respectively. Figure 1A shows the ROC curve of each index to predict postpartum depression in patients with pregnancy-induced hypertension.

Construction of nomogram model

The independent risk factors for postpartum depression in patients with pregnancy-induced hypertension were used as predictors to construct a nomogram model (Figure 2). The internal verification was carried out by bootstrap self-sampling 500 times. The slope of the calibration curve was similar to that of the diagonal line, suggesting that the degree of fitting between the calibration curve and the ideal curve was high, indicating that there was no significant difference between the predicted and measured values. The average absolute error (0.037) was small, which suggested that the nomogram model had a predictive effect (Figure 3).

ROC curve analysis of nomogram model prediction

The AUC predicted by the nomogram for each index was 0.867 greater than the AUC of each index in Figure 1A. The specificity and sensitivity were 0.676 and 0.889, respectively. The Hosmer–Lemeshow test statistic was 10.739, and there was no significant difference between the predicted value and actual ($P = 0.217$) (Figure 1B).

Table 1 Comparison of clinical data of patients with pregnancy-induced hypertension

Variables	Depression group (*n* = 54)	Non-depression group (*n* = 222)	t/χ^2/Z	*P* value
Gestational weeks of pregnancy-induced hypertension			-2.902	0.004
< 28	20 (37.04)	58 (26.13)		
28–34	30 (55.56)	100 (45.05)		
> 34	4 (7.41)	64 (28.83)		
Adverse birth outcomes			16.283	< 0.001
Yes	16 (29.63)	20 (9.01)		
No	38 (70.37)	202 (90.99)		
History of adverse childbirth			0.310	0.578
Yes	8 (14.81)	40 (18.02)		
No	46 (85.19)	182 (81.98)		
Family support status			-3.349	0.001
Very little or no support	6 (11.11)	4 (1.80)		
General support	26 (48.15)	78 (35.14)		
Full support	22 (40.74)	140 (63.06)		
VAD during pregnancy and puerperium			29.504	< 0.001
Yes	14 (25.93)	8 (3.60)		
No	40 (74.07)	214 (96.40)		
Complications			12.325	< 0.001
Yes	28 (51.85)	60 (27.03)		
No	26 (48.15)	162 (72.97)		
Asthma during pregnancy			3.140	0.076
Yes	10 (18.52)	22 (9.91)		
No	44 (81.48)	200 (90.09)		
Family history of hypertension			15.471	< 0.001
Yes	12 (22.22)	12 (5.41)		
No	42 (77.78)	210 (94.59)		
Mode of delivery			-0.285	0.775
Cesarean section	16 (29.63)	74 (33.33)		
Natural birth	32 (59.26)	120 (54.05)		
Vaginal midwifery	6 (11.11)	28 (12.61)		
Number of deliveries (times)			0.591	0.442
1 (primiparous)	32 (59.26)	144 (64.86)		
≥ 2 (multiparous)	22 (40.74)	78 (35.14)		
Education level			-1.490	0.136
High school and below	18 (33.33)	52 (23.42)		
Junior college	24 (44.44)	106 (47.75)		
Bachelor's degree and above	12 (22.22)	64 (28.83)		
Plan a pregnancy			0.409	0.522
No	10 (18.52)	50 (22.52)		

Yes	44 (81.48)	172 (77.48)		
Occupational status during pregnancy			-0.459	0.646
Not in office	10 (18.52)	50 (22.52)		
Intermittent rest	32 (59.26)	124 (55.86)		
On-the-job	12 (22.22)	48 (21.62)		
Feeding methods			-0.180	0.857
Artificial feeding	10 (18.52)	46 (20.72)		
Mixed feeding	24 (44.44)	94 (42.34)		
Pure breastfeeding	20 (37.04)	82 (36.94)		
5-HTR1AC (-1019) G				
Genotype			-1.269	0.205
GG	30 (55.56)	117 (52.70)		
CG	12 (22.22)	17 (7.66)		
CC	12 (22.22)	88 (39.64)		
Allelic			3.676	0.055
G	72 (66.67)	251 (56.63)		
C	36 (33.33)	193 (43.47)		
Intestinal flora imbalance during pregnancy and childbirth			16.283	< 0.001
Yes	16 (29.63)	20 (9.01)		
No	38 (70.37)	202 (90.99)		
Weight gain in late pregnancy			-2.122	0.034
Increase excess	22 (40.74)	44 (19.82)		
Insufficient increase	12 (22.22)	80 (36.04)		
Adequate increase	20 (37.04)	98 (44.14)		
Age (years)	33.25 ± 9.46	32.87 ± 10.64	0.240	0.810
Maternal family monthly income (yuan)	3766.15 ± 1348.26	4200.85 ± 1622.26	1.821	0.070
EPA (pg/mL)	1.75 ± 0.31	2.02 ± 0.33	7.475	< 0.001
DHA (pg/mL)	1.83 ± 0.27	2.08 ± 0.36	4.784	< 0.001
AA (lgx, pg/mL)	1.08 ± 0.25	0.98 ± 0.36	1.930	0.055
Hs-CRP (mg/L)	21.57 ± 5.39	22.04 ± 5.12	0.599	0.550
PCT (μg/L)	2.02 ± 0.59	1.95 ± 0.46	0.946	0.345

VAD: Vitamin A deficiency; 5-HTR1AC(-1019)G: 5-HT1A receptor gene C(-1019)G; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; AA: Arachidonic acid; hs-CRP: High-sensitivity C-reactive protein; PCT: Procalcitonin.

DISCUSSION

Postpartum depression in patients with pregnancy-induced hypertension can cause neurological and endocrine system disorders, often making them lose their ability to care for themselves and their infants, which is not conducive to them and their infant's health[9]. Other studies have shown that for infants aged 1.5-2 mo, maternal postpartum depression may lead to developmental delays in gross motor, fine motor, and communication areas. Research has suggested that postpartum depression harms mothers and adversely affects children's cognition, behaviour, temperament, and physical development[10]. The risk of postpartum depression in patients with pregnancy-induced hypertension is higher than that in normal pregnant, which may be related to many factors such as VAD during pregnancy and puerperium, family history of hypertension, and intestinal flora imbalance during pregnancy and puerperium. Therefore, integrating the risk factors for postpartum depression in patients with pregnancy-induced hypertension is of clinical significance for identifying high-risk patients.

Table 2 Assignment

Variable	Assignment
Gestational weeks of pregnancy-induced hypertension	0 > 34; 1, 28–34; 2 < 28.
Adverse birth outcomes	0 = No, 1 = Yes
Family support status	0 = full support, 1 = general support, 2 = little or no support
VAD during pregnancy and puerperium	0 = No, 1 = Yes
Complications	0 = none, 1 = have
Family history of hypertension	0 = none, 1 = have
Intestinal flora imbalance during pregnancy and childbirth	0 = none, 1 = have
Weight gain in late pregnancy	0 = increase sufficient, 1 = increase insufficient, 2 = increase excessive
EPA	Actual value
DHA	Actual value

VAD: Vitamin A deficiency; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

Table 3 Multivariate logistic regression analysis of postpartum depression in patients with pregnancy-induced hypertension

Independent variable	*B*	Wald	SE	*P* value	OR (95%CI)
Gestational weeks of pregnancy-induced hypertension	-	-	4.062	0.131	-
No. of weeks of pregnancy (1)	-1.564	0.816	3.678	0.055	0.209 (0.042–1.035)
Gestational weeks of pregnancy-induced hypertension (2)	-0.592	0.457	1.677	0.195	0.553 (0.226–1.355)
Adverse birth outcomes	0.261	0.684	0.145	0.703	1.298 (0.340–4.959)
Family support status	-	-	1.545	0.462	-
Family support status (1)	-1.365	1.155	1.397	0.237	0.255 (0.027–2.456)
Family support status (2)	-0.630	0.898	0.492	0.483	0.533 (0.092–3.095)
VAD during pregnancy and puerperium	2.159	0.642	11.296	0.001	8.662 (2.459–30.506)
Complications	-0.526	0.73	0.520	0.471	0.591 (0.141–2.470)
Family history of hypertension	1.868	0.675	7.667	0.006	6.474 (1.726–24.289)
Intestinal flora imbalance during pregnancy and childbirth	1.877	0.559	11.273	0.001	6.535 (2.185–19.551)
Weight gain in late pregnancy	-	-	4.060	0.131	-
Weight gain in late pregnancy (1)	-0.977	0.490	3.980	0.046	0.377 (0.144–0.983)
Weight gain in late pregnancy (2)	-0.359	0.538	0.446	0.504	0.698 (0.243–2.003)
EPA	-3.125	0.780	16.04	< 0.001	0.044 (0.010–0.203)
DHA	-2.568	0.644	15.88	< 0.001	0.077 (0.022–0.271)

VAD: Vitamin A deficiency; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

The postpartum depression incidence in 138 patients with pregnancy-induced hypertension was 19.57%, similar to previous studies[11]. Multivariate logistic regression analysis showed that patients with pregnancy-induced hypertension and VAD during pregnancy and puerperium, family history of hypertension, maternal intestinal flora imbalance, low EPA level, or low DHA level had an increased risk of postpartum depression. We speculated that progesterone level in pregnant women in early pregnancy decreases. Because progesterone can promote the release of VA stored in the liver and adipose tissue into blood, this function of progesterone is weakened after progesterone deficiency, resulting in a decrease in serum VA concentration and the development of VAD. VAD during puerperium may also be related to insufficient progesterone secretion. Long-term continuous VAD during pregnancy and puerperium can promote postpartum depression[12]. In the present study, the proportion of VAD during pregnancy and puerperium in depressed patients was higher than in non-depressed patients, indicating that perinatal VAD also increased the risk of postpartum depression in patients with pregnancy-induced hypertension. There is no consensus on the mechanism of VAD in

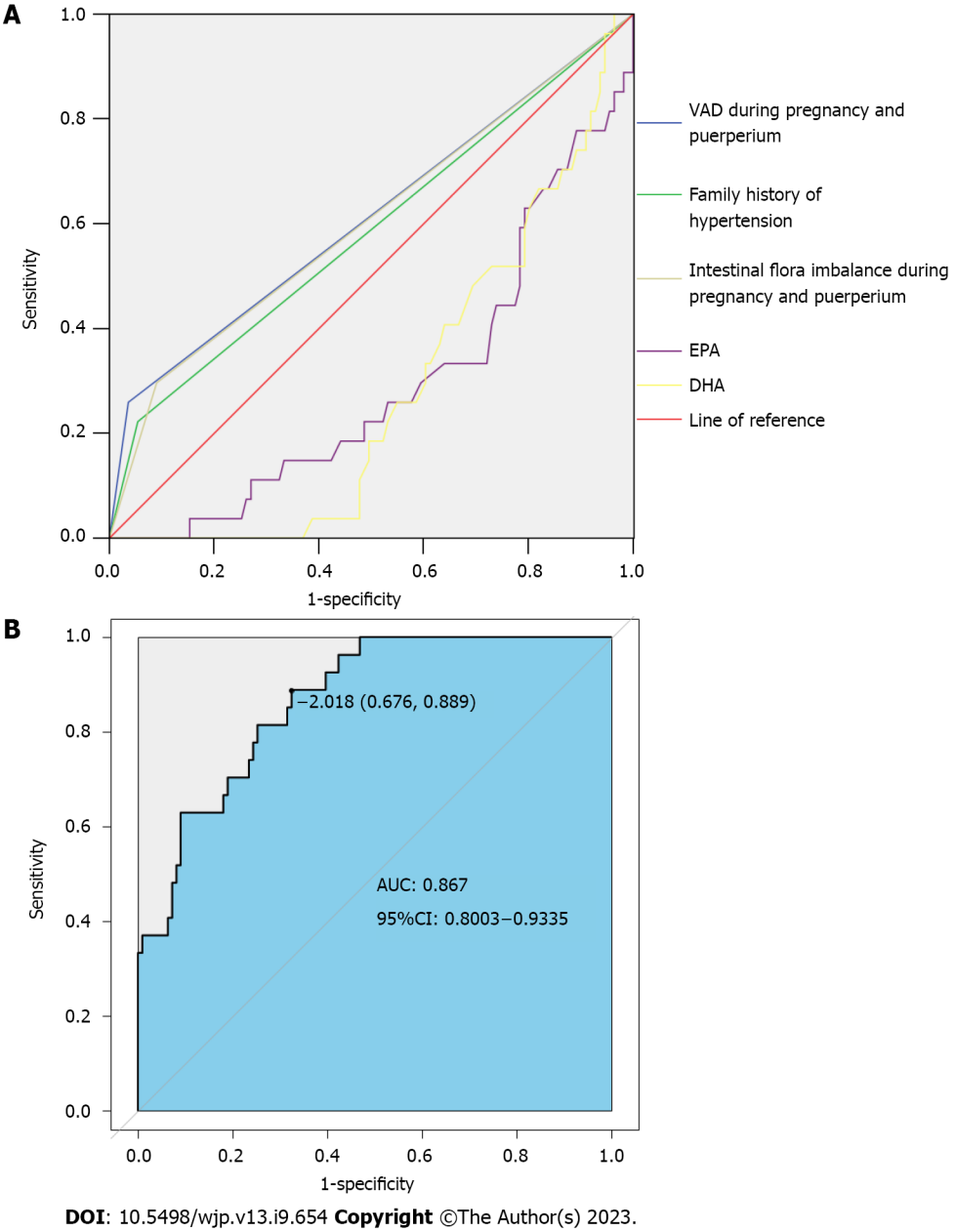

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Figure 1 Receiver operating characteristic curve. A: each index in predicting postpartum depression in patients with pregnancy-induced hypertension; B: The graph model predicting the risk of postpartum depression in pregnancy-induced hypertension. EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

postpartum depression development. Some scholars believe that VA can affect the proliferation and differentiation of nerve cells, synapse formation, and axon growth. Studies have also found that VAD may be the basis of the pathogenesis of Alzheimer's disease, which can increase hippocampal Aβ deposition, resulting in hippocampal plasticity and memory function[13]. Therefore, VA is involved in related activities of cranial nerves. These activities may be factors that maintain a good mood. Once the body has continuous VAD, it may increase the incidence of depression. For pregnancy-induced hypertension patients with a family history of hypertension, the psychological burden may be aggravated by similar diseases in their relatives, resulting in anxiety, such as poor pregnancy and poor fetal birth due to unsatisfactory blood pressure control, so it is more likely to induce postpartum depression. Research has also shown a significant difference in the family history of hypertension between the postpartum depression group and the non-depression group of pregnant women with gestational hypertension[14], which is consistent with the results of our study. In recent years, more studies on the mechanism of postpartum depression have shifted from social environmental factors to biological factors (such as gene polymorphism). Abnormal intestinal flora structure can cause abnormal fluctuations in the central nervous system, thus promoting the occurrence of mental diseases such as depression. Intestinal flora imbalance can induce an immune response, and then the hypothalamus-pituitary-adrenal (HPA) axis is abnormally active, and depression occurs. Relevant studies have also shown that after bifidobacteria supplementation to people with intestinal flora imbalance, the HPA axis activity weakens. Also, the concentration of neurotrophic factors in the brain that regulate neuronal development increases, and the HPA axis improves[15]. Therefore, intestinal flora imbalance is a risk factor for postpartum depression in patients with pregnancy-induced hypertension. Clinically, we can reduce the occurrence of postpartum depression by

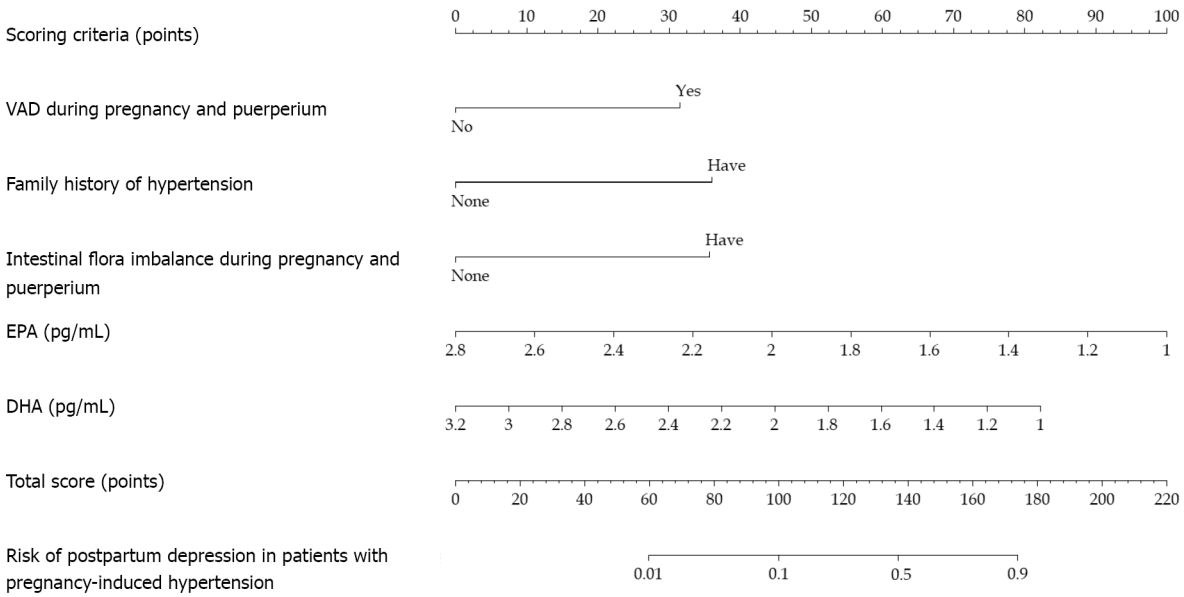

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Figure 2 Nomogram model of postpartum depression in patients with pregnancy-induced hypertension. EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

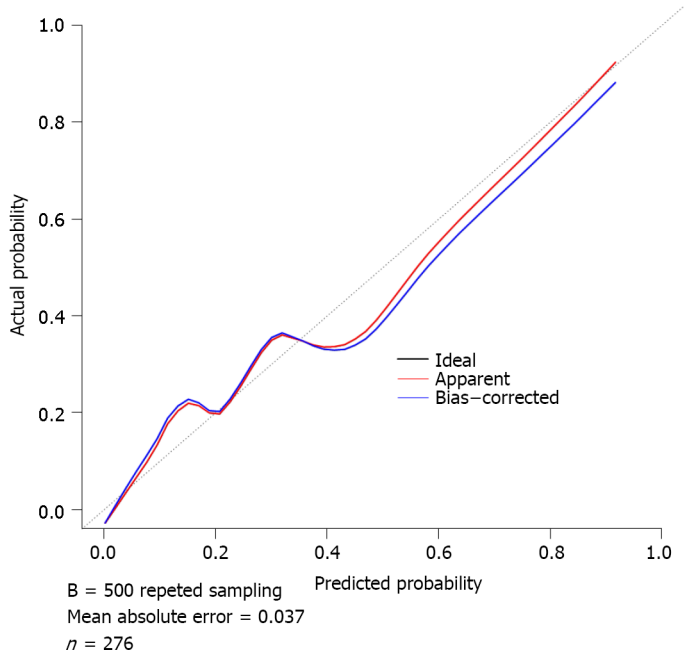

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Figure 3 Correction curve.

improving the composition of intestinal flora in patients with pregnancy-induced hypertension. EPA and DHA are fatty acids with multiple double bonds and are chief components of phospholipids in the human brain. Phospholipids ensure the integrity and fluidity of nerve cell membranes and participate in the signal transduction of various substances in nerve cells. Therefore, EPA and DHA are closely related to the brain's nervous system. The lack of both may cause neurological and psychological disorders and damage the cerebellum, vision, and cognition. The lower the level of EPA or DHA, the more prone patients are to depression. Serum EPA and DHA levels affect the formation of postpartum depression and negative correlation[16,17]. These show that ensuring adequate EPA or DHA intake during pregnancy may be a protective factor for postpartum depression in patients with pregnancy-induced hypertension. This study also analyzed the 5-HTR1AC (-1019) G genotype and allele in patients with pregnancy-induced hypertension. The results showed that there was no difference in the gene polymorphism of this locus between patients with postpartum depression and non-depressed patients, which was inconsistent with relevant research[18]. It may be related to the

different sample sizes and inclusion/exclusion criteria of the two studies. Therefore, we speculated that the occurrence of postpartum depression in patients with pregnancy-induced hypertension may be slightly influenced by biological factors.

This study summarized the risk factors related to postpartum depression in patients with pregnancy-induced hypertension and applied these five risk factors as predictive variables to construct a predictive nomogram model. After the model verification, we found that the degree of fitting between the calibration and the ideal curve was high. The AUC predicted by the nomogram model was higher, indicating that the model had better discriminant ability. The Hosmer–Lemeshow test showed that the predictive data of the model were not much different from the actual data, suggesting that the model had high calibration or predictive accuracy. The nomogram model showed the relationship between the five variables of VAD during pregnancy and puerperium, family history of hypertension, intestinal flora imbalance during pregnancy and puerperium, EPA, and DHA with the calibrated lines, which was readable and easy to evaluate. This study explored the nomogram model of postpartum depression in post-inflammatory hyperpigmentation (PIH) patients, which can help clinicians quickly and accurately identify patients with PIH who are at risk of depression after high production, help guide them to take targeted intervention measures, and thus reduce the possibility of postpartum depression in patients. It has high clinical application value.

There were some limitations to this study. All the women were from a single centre, and there may have been potential selection bias. The risk prediction nomogram model for postpartum depression in patients with pregnancy-induced hypertension was only internally validated, and there was a lack of external validation from other central data. Therefore, we need sufficient external evidence before the practical application of the model.

CONCLUSION

Postpartum depression in patients with pregnancy-induced hypertension is affected by VAD during pregnancy and puerperium, family history of hypertension, intestinal flora imbalance during pregnancy, and puerperium, EPA, and DHA. The established nomogram model can effectively assess its risk.

ARTICLE HIGHLIGHTS

Research background

The clinical prediction of postpartum depression in patients with pregnancy-induced hypertension is still insufficient, and the application of the nomogram model in predicting postpartum depression in patients with pregnancy-induced hypertension is rarely reported.

Research motivation

Compared with normal pregnant, pregnancy-induced hypertension patients have a higher risk of postpartum depression, which is related to several factors. By integrating risk factors of postpartum depression in pregnancy-induced hypertension and constructing predictive models, this study guides identifying high-risk patients and early clinical intervention.

Research objectives

The study's purpose was to integrate the risk factors of postpartum depression in patients with pregnancy-induced hypertension, construct a graph prediction model, and evaluate the predictive effect of the model.

Research methods

Multivariate logistic regression analysis and LASSO regression were used to analyze the factors related to postpartum depression in pregnancy-induced hypertension. R version 4.0.3 was used to construct a line graph risk predictive model. The area under the receiver operating curve was used to evaluate effectiveness.

Research results

Vitamin A deficiency (VAD) during pregnancy and puerperium, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are independent risk factors for postpartum depression in pregnancy-induced hypertension. The histogram model established by this method had good predictive efficacy and could guide clinical prevention and intervention.

Research conclusions

Postpartum depression in pregnancy-induced hypertension is related to VAD during pregnancy and puerperium, family history of hypertension, intestinal flora disorders during pregnancy and perinatal period, EPA, and DHA. The predictive efficacy of the risk model established by this method has clinical application value.

Research perspectives

Future research directions should increase the sample size or multicenter study to verify the results, enhance the reliability of the conclusions, and better carry out clinical prevention interventions.

FOOTNOTES

Author contributions: Pan JW designed and performed the research and wrote the paper; Zhao G designed the research and supervised the report.

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Informed consent statement: Approved and exempted from informed consent.

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ORIGINAL ARTICLE

Retrospective Study

Immune function, gastrointestinal hormone levels, and their clinical significance in patients with gastric ulcers complicated with depression

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Abstract

BACKGROUND

Gastric ulcer (GU) is a common digestive tract disease, and medical records of GU combined with depression are increasingly common. Currently, the risk factors and pathogenesis of GU complicated with depression remain unclear. Low immune function and gastrointestinal hormone levels may also be significant risk factors. Therefore, this study explored the immune function and gastrointestinal hormone levels in patients with GU combined with depression.

AIM

To explore the immune function, gastrointestinal hormone level, and clinical significance of patients with GU combined with depression.

METHODS

A retrospective analysis was conducted on 300 patients with GU combined with depression admitted to Guizhou Provincial People's Hospital from January 2021 to June 2022 as the study subjects. According to the Hamilton Depression Scale (HAMD) score, patients were divided into mild-to-moderate (n = 210) and heavy (n = 90) groups. Basic data, immune function indices [immunoglobulin A (IgA), IgM, IgG, serum $CD4^+$ and $CD8^+$ percentage, and $CD4^+/CD8^+$ ratio], and gastrointestinal hormone indices [serum gastrin (GAS), cholecystokinin (CCK), and motilin (MTL) levels] were collected. The basic data of the two groups were compared, and the immune function and gastrointestinal hormone indices were analyzed. Multivariate logistic regression was used to analyze the factors influen-

cing the severity of GU complicated with depression. The receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were used to analyze the value of the immune function index, gastrointestinal hormone index, and combined index in predicting the severity of GU complicated with depression.

RESULTS

There were no marked differences in sex, age, body mass index, abdominal distension, abdominal pain, belching, nausea, vomiting, or sleep disorders between the heavy and mild-to-moderate groups ($P > 0.05$). There was a marked difference in the family history of depression between the heavy and mild-to-moderate groups ($P < 0.05$). There were significant differences in serum IgA and IgM levels and serum $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ ratios between the heavy and mild-to-moderate groups ($P < 0.05$). Multivariate analysis showed that IgA, IgM, GAS, and CCK serum levels influenced the severity of GU with depression ($P < 0.05$). The AUC of the ROC curve for serum IgA level predicting GU with depression severity was 0.808 [95% confidence interval (CI): 0.760-0.857], the AUC of the serum IgM level was 0.757 (95%CI: 0.700-0.814), the AUC of the serum GAS level was 0.853 (95%CI: 0.810-0.897), the AUC of the serum CCK level was 0.762 (95%CI: 0.709-0.822), the AUC of immune function (IgA, IgM) and gastrointestinal hormone levels (GAS, CCK) for the prediction of GU with depression severity was 0.958 (95%CI: 0.933-0.976).

CONCLUSION

Important factors influencing GU complicated with depression are serum IgA, IgM, GAS, and CCK indicators. They can be used as indicators to predict the severity of GU complicated with depression.

Key Words: Gastric ulcer combined with depression; Immune function; Gastrointestinal hormones

Core Tip: The occurrence and severity of gastric ulcer (GU) combined with depression may be related to autoimmune dysfunction and gastrointestinal hormone levels. In this study, multivariate logistic regression analysis was used to influence the severity of concurrent depression in GU. The results suggest that impaired T cell function and gastrointestinal hormone disorders may directly affect the development and development of depression. In addition, the immune function indicators combined with gastrointestinal hormone levels predict high AUC, specificity and sensitivity, which has a very good reference value.

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INTRODUCTION

With the continuous development of living standards, people's eating and living habits have changed to varying degrees; however, poor living habits have had a greater impact on people's health. Gastric ulcers (GU) are common digestive system diseases. The occurrence and continuous progression of the disease are related to the dynamic balance between gastric mucosal defense and invasion factors. *Helicobacter pylori* (*H. pylori*) infection, excessive gastric acid secretion, and adverse drug factors are all influencing factors that cause GU[1,2]. Gastric juice concentration in patients with GU stimulates the gastric mucosa, promotes changes in the gastric structure and environment, causes serious damage to the gastric mucosa, and causes long-term stay of pathogenic factors, resulting in the long-term treatment of the disease[3]. Clinical manifestations of GU include stomach and abdominal pain, heartburn, acid reflux, among others. The symptoms worsen after eating irritating foods or foods that are hard to digest. Smoking and alcohol consumption can also cause GU. Patients with severe GU often experience gastric perforation and gastric bleeding[4].

Recently, psychophysiological factors have been significant in the pathogenesis of gastrointestinal illnesses. GU are characterized by repeated attacks that can easily cause adverse severe psychological states. Some patients also experience anxiety and depression due to a lack of timely and effective treatment for physical illness, which makes depression increasingly prominent in GU patients[5]. Anti-*H. pylori* therapy, drugs controlling excessive gastric acid secretion, and protecting gastric mucosa are primarily used for the clinical treatment of GU. The impact of psychological factors on disease occurrence and progression in clinical practice is often overlooked, which makes it difficult to treat patients comprehensively[6]. Relevant data show that poor psychological status may increase the risk of digestive disorders[7]; however, there are few studies on patients with GU associated with depression. Exploring the factors influencing GU combined with depression is important for clinical treatment and the improvement of patients' quality of life. Studies have shown that the occurrence of GU combined with depression may be related to abnormal autoimmune function and disorders of gastrointestinal hormone levels[8]; however, the specific mechanism is not clear. Due to the decrease in gas-

trointestinal function and food intake, GU complicated with depression is often accompanied by a decline in immune function, and the adverse psychological state aggravates the risk of malnutrition. The intestinal mucosal barrier and immune function are extremely poor, which increases the risk of depression. Therefore, 300 patients with GU and depression were included in this study to explore their immune function, gastrointestinal hormone levels, and clinical significance, to provide a reference for reducing the incidence of GU complicated by depression.

MATERIALS AND METHODS

Patient characteristics

A retrospective analysis was conducted to select 300 patients with GU complicated with depression admitted to Guizhou Provincial People's Hospital from January 2021 to June 2022 as the study subjects. Inclusion criteria: (1) Age ≥ 18 years old; (2) All patients have nausea, stomach pain, and acid reflux symptoms; and (3) The basic information and laboratory indicators of all patients are complete. The exclusion criteria were as follows: (1) Patients with malignant tumors or chronic atrophic gastritis and other gastrointestinal illnesses; (2) Patients who had undergone gastrointestinal surgery in the past 3 mo; (3) Patients with organic disorders; and (4) Patients with autoimmune diseases and systemic inflammatory diseases.

Diagnostic criteria for GU[9]: GU was confirmed by endoscopy, and the pathological diagnosis of *H. pylori* infection was positive. Diagnostic criteria for depression[10]: Diagnostic criteria for depression in the Diagnostic and Statistical Manual of Mental Disorders were employed. The diagnosis was based on the patient's low mood, slow thinking, reduced language, movements, suspected illness, insomnia, loss of interest, and related symptoms lasting more than 2 wk. The severity of the disease and the degree of social function impairment increase with the number of symptoms.

Grouping method

All patients on the day of admission, patients were routinely assessed using the Hamilton Depression Scale (HAMD)[11], And were graded according to the HAMD scale: A score of 7 points indicates no depression, > 8-19 points indicates depression, > 20-34 points indicates mild to moderate depression, and > 35 points indicates major depression. All enrolled patients with GU and depression were divided into mild-to-moderate (n = 210) and heavy (n = 90) groups.

Clinical data collection

Clinical data collection: (1) Basic information: Sex, age, body mass index (BMI), abdominal distension, abdominal pain, belching, nausea, vomiting, sleep disorders, and family history of depression; (2) Immune function index: The levels of serum immunoglobulin A (IgA), IgM, and IgG were detected by immunoturbidimetry (the kit was purchased from Lifotronic Technology Co., Ltd.). The percentages of serum $CD4^+$ and $CD8^+$ cells were detected using a Beckman CytoFLEX flow cytometer and a supporting kit (Beckman Coulter), and the ratio of $CD4^+/CD8^+$ cells was calculated; and (3) Gastrointestinal hormone indices: The levels of serum gastrin (GAS), cholecystokinin (CCK), and motilin (MTL) were detected by ELISA (the kit was purchased from MLBIO Enzyme Linked Biology).

Statistical analysis

Data analysis was performed using SPSS statistical software 24.0. The measurement data conforming to the normal distribution were expressed as mean ± SD and analyzed by t-test. Count data is expressed as frequency percentage (n%) by the χ^2 test. Multivariate logistic regression analysis was used to explore factors influencing the severity of GU complicated with depression. The receiver operating characteristic curve (ROC) and area under the ROC curve (AUC) were used to analyze the value of the immune function index, gastrointestinal hormone index, and combined index in predicting the severity of GU complicated with depression, and the specificity and sensitivity were calculated. Test level: α = 0.05.

RESULTS

Basic data analysis

Figure 1 shows the number of patients, the number of patient inclusion, and the flow chart of the analysis method. There was no significant difference in gender, age, BMI, abdominal distension, abdominal pain, belching, nausea, vomiting, and sleep disorders between the heavy group and the mild to moderate group (P > 0.05). There was statistically significant difference in family history of depression between severe group and mild to moderate group (P < 0.05) (Table 1).

Comparison of the immune function indicators between the two groups

There were significant differences in serum IgA and IgM levels and serum $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ ratios between the heavy and mild-to-moderate groups (P < 0.05). There was no significant difference in serum IgG level between the two groups (P > 0.05) (Table 2).

Comparison of the gastrointestinal hormone indexes

Serum GAS and CCK levels were compared between the severe and mild-to-moderate groups (P < 0.05), and there was no difference in serum MTL levels between the two groups (P > 0.05) (Table 3).

Table 1 Comparison of general data [*n* (%), mean ± SD]

Feature	Heavy group (*n* = 90)	Mild to moderate group (*n* = 210)	χ^2/t value	*P* value
Gender (male/female)	48/42	109/101	0.052	0.820
Age (yr)	45.29 ± 4.56	46.37 ± 5.44	-1.773	0.078
BMI (kg/m^2)	22.48 ± 2.17	22.19 ± 2.13	1.114	0.266
Abdominal distension (Yes/No)	51/39	102/108	1.652	0.199
Abdominal pain (Yes/No)	43/47	100/110	0.001	0.980
Belching (Yes/No)	40/50	107/103	1.068	0.301
Nausea (Yes/No)	38/52	98/112	0.502	0.479
Vomiting (Yes/No)	46/44	105/105		
Sleep disorder (Yes/No)	47/43	85/125	3.528	0.060
Family history of depression (Yes/No)	45/45	48/162	21.699	< 0.001

BMI: Body mass index.

Table 2 Comparison of immune function indicators between the two groups (mean ± SD)

Index	Heavy group (*n* = 90)	Mild to moderate group (*n* = 210)	*T* value	*P* value
IgA (g/L)	1.86 ± 0.42	2.54 ± 0.63	-10.791	< 0.001
IgM (g/L)	2.97 ± 0.62	3.59 ± 0.65	-7.698	< 0.001
IgG (g/L)	15.37 ± 3.48	15.42 ± 3.52	-0.113	0.910
$CD4^+$ (%)	32.16 ± 5.31	38.48 ± 5.49	-9.218	< 0.001
$CD8^+$ (%)	29.37 ± 3.52	23.59 ± 3.13	6.800	< 0.001
$CD4^+/CD8^+$ ratio	1.24 ± 0.27	1.67 ± 0.36	-11.104	< 0.001

IgA: Immunoglobulin A; IgM: Immunoglobulin M; IgG: Immunoglobulin G.

Table 3 Comparison of gastrointestinal hormone indexes between the two groups (mean ± SD)

Group	*n*	GAS (pg/mL)	CCK (ng/L)	MTL (pg/mL)
Heavy group	90	43.52 ± 5.79	154.49 ± 11.68	256.28 ± 13.12
Mild to moderate group	210	52.44 ± 6.23	167.25 ± 13.54	258.18 ± 20.47
t value		-11.598	-7.781	-0.960
P value		< 0.001	< 0.001	0.338

GAS: Gastrin; CCK: Cholecystokinin; MTL: Motilin.

Multivariate analysis affecting the severity of GU combined with depression

The above statistically significant indicators (family history of depression, IgA, IgM, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ ratio, GAS, and CCK) were used as independent variables, and GU combined with depression severity as the dependent variable (see Table 4). Multivariate analysis showed that serum IgA, IgM, GAS, and CCK levels influenced the severity of GU complicated with depression ($P < 0.05$) (Table 5).

ROC curve of immune function predicting GU with depression severity

The AUC of the ROC curve of serum IgA level for predicting GU with depression severity was 0.808 [95% confidence interval (CI): 0.760-0.857], sensitivity was 0.738, and specificity was 0.778, The AUC of the serum IgM level was 0.757 (95%CI: 0.700-0.814), with a sensitivity of 0.748 and a specificity of 0.700 (Figure 2A).

Table 4 The assignments of related indicators

Index	Code	Description of valuation
Family history of depression	X1	1 = Yes; 0 = No
IgA	X2	Enter actual value
IgM	X3	Enter actual value
$CD4^+$	X4	Enter actual value
$CD8^+$	X5	Enter actual value
$CD4^+/CD8^+$ ratio	X6	Enter actual value
GAS	X7	Enter actual value
CCK	X8	Enter actual value

IgA: Immunoglobulin A; IgM: Immunoglobulin M; GAS: Gastrin; CCK: Cholecystokinin.

Table 5 Multi-factor analysis

Index	β	SE	Wald χ^2	*P* value	OR (95%CI)
Family history of depression	0.744	0.551	1.822	1.770	2.103 (0.714-6.193)
IgA	-2.703	0.600	20.313	< 0.001	0.067 (0.021-0.217)
IgM	-1.509	0.487	9.586	0.002	0.221 (0.085-0.575)
$CD4^+$	0.151	0.218	0.482	0.488	1.163 (0.759-1.782)
$CD8^+$	-0.286	0.290	0.969	0.325	0.751 (0.425-1.327)
$CD4^+/CD8^+$ ratio	-9.136	5.432	12.829	0.093	0.000 (0.000-4.525)
GAS	0.267	0.050	28.147	< 0.001	0.766 (0.694-0.845)
CCK	0.093	0.024	15.137	< 0.001	0.911 (0.869-0.955)
Constant	52.073	10.637	23.963	< 0.001	-

IgA: Immunoglobulin A; IgM: Immunoglobulin M; GAS: Gastrin; CCK: Cholecystokinin; OR: Odds ratio; CI: Confidence interval.

The ROC curve of gastrointestinal hormones in predicting GU combined with depression severity

The AUC of the ROC curve of serum GAS level predicting GU with depression severity was 0.853 (95%CI: 0.810-0.897), sensitivity was 0.814, and specificity was 0.767, The AUC of serum CCK level was 0.762 (95%CI: 0.709-0.822), with a sensitivity of 0.590 and a specificity of 0.844 (Figure 2B).

ROC curve of immune function combined with gastrointestinal hormone levels in predicting GU combined with depression severity

The AUC of immune function (IgA, IgM) combined with gastrointestinal hormone levels (GAS, CCK) predicting GU with depression severity was 0.958 (95%CI: 0.933-0.976), sensitivity was 0.967, and specificity was 0.829 (Figure 2C).

DISCUSSION

GU refers to the ulcer formed in the gastric angle, gastric antrum, cardia, and hiatal hernia. It is a gastric mucosal injury that is caused by various factors. It can be caused by *H. pylori* infection, drugs, heredity, diet, and other factors and is often accompanied by acid reflux, belching, abdominal distension, and upper abdominal pain symptoms[12]. The related study showed that the occurrence of GU is caused by the process of 'attack factor' or the weakening of 'defense factor'; the "attack factor" includes gastric acid, pepsin, *H. pylori*, among others, and the "defense factor" includes gastric mucosa, gastric mucus, bicarbonate, among others[13]. It has been found that *H. pylori* infection is the most common cause of GU. *H. pylori* can damage the protective layer of the gastric mucosa, thus accelerating the occurrence of gastric mucosal lesions, easily causing various complications, and threatening the physical and mental health of patients[14]. GU combined with depression is a typical digestive tract illness in clinical medicine, and gastric acid secretion in the human body is associated with psychological pressure. Patients are affected by psychological and physiological factors, and inner

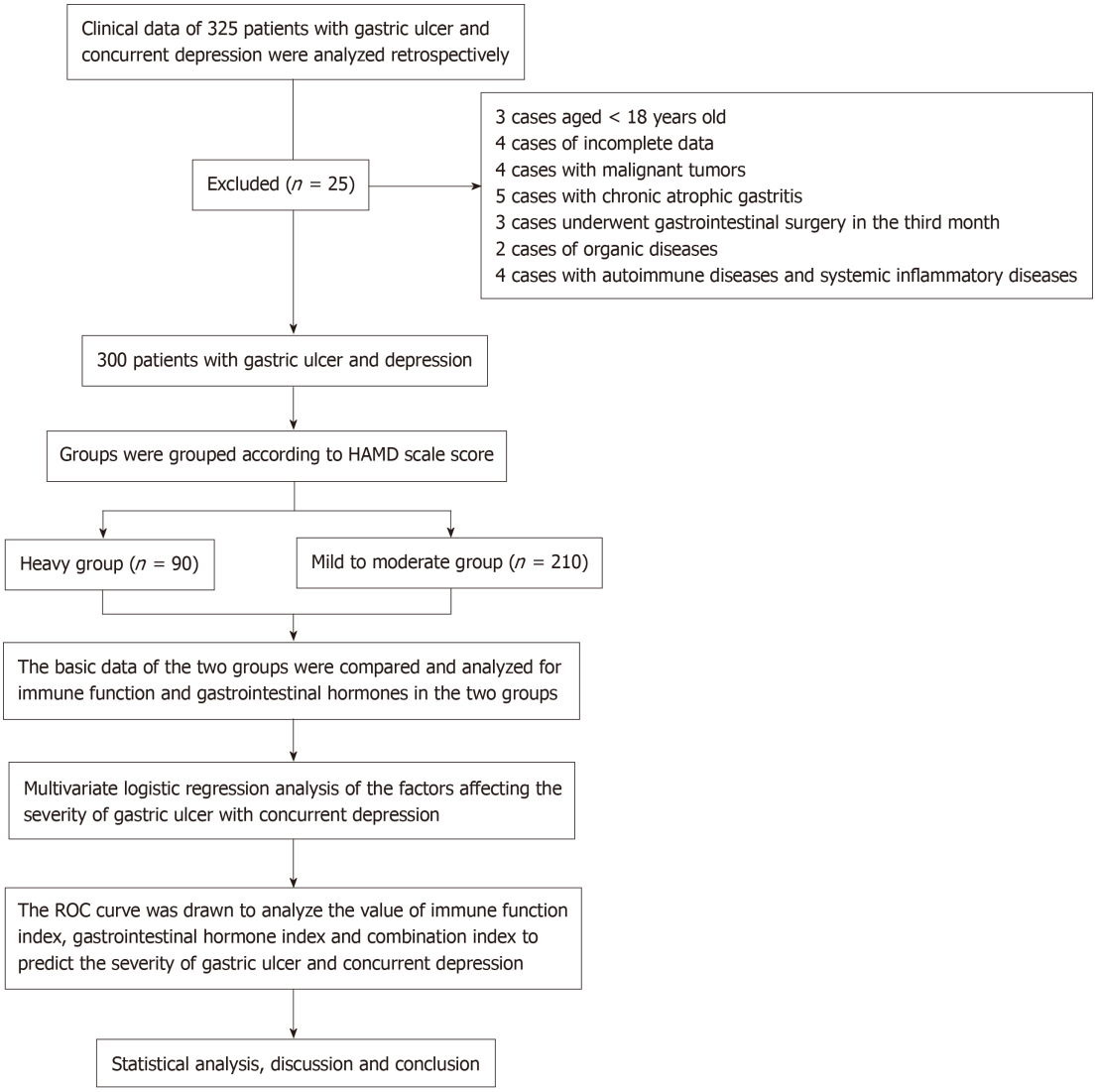

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Figure 1 The number of patients, the number of patients included, and the flow chart of the analysis method. HAMD: Hamilton Depression Scale; ROC: Receiver operating characteristic.

tension and nervous system pressure can cause GUs. The incidence of psychosocial abnormalities has increased in recent years and exists as a comorbidity of other basic and chronic diseases, with these two factors influencing each other[15].

Depression is a primary emotional and common mood disorder. Its incidence ranks second in the incidence of various diseases worldwide. Furthermore, it is found that patients with various chronic diseases have anxiety and depression, and the mortality rate of patients with heart disease complicated with depression is higher than that of patients with simple depression, so the treatment of patients with depression is necessary[16]. The National Institute of Mental Health showed that the prevalence of mental disorders in patients with somatic diseases is as high as 41%[17]. Therefore, while paying clinical attention to the diagnosis and treatment of physical diseases, we should also pay attention to mental and psychological interventions, as the number of patients with GU complicated with depression in China has increased annually[18]. Several factors affect the pathogenesis of GU, which is complicated with depression. Autoimmune dysfunction and gastrointestinal hormone disorders may be important factors affecting disease severity; however, this hypothesis remains controversial. Therefore, it is necessary to explore the importance of immune function and gastrointestinal hormone indices in patients with GU or depression.

In this study, all selected patients were scored using the HAMD. Among them, 210 patients with mild to moderate GU complicated with depression, accounting for 70%, and 90 patients in the heavy group, accounting for 30%. Studies have shown that disease characteristics and severity of depression are influenced by a family history of affective disorder[19]. In this study, the mild-to-moderate and heavy groups had a family history of depression. This indicates that patients with a family history of depression may have more severe anhedonia and anxiety symptoms and that these mood disorders can potentially affect immune function and gastrointestinal hormone levels. The pathogenesis of GU is closely associated with immune deficiency[20]. Depression and anxiety can cause digestive system diseases. Long-term mental disorders overstretch the nervous system, leading to gastrointestinal hormone secretion disorders and excessive sensitivity to food stimulation. Patients with GU and depression have weakened gastrointestinal motility, delayed gastric emptying, and

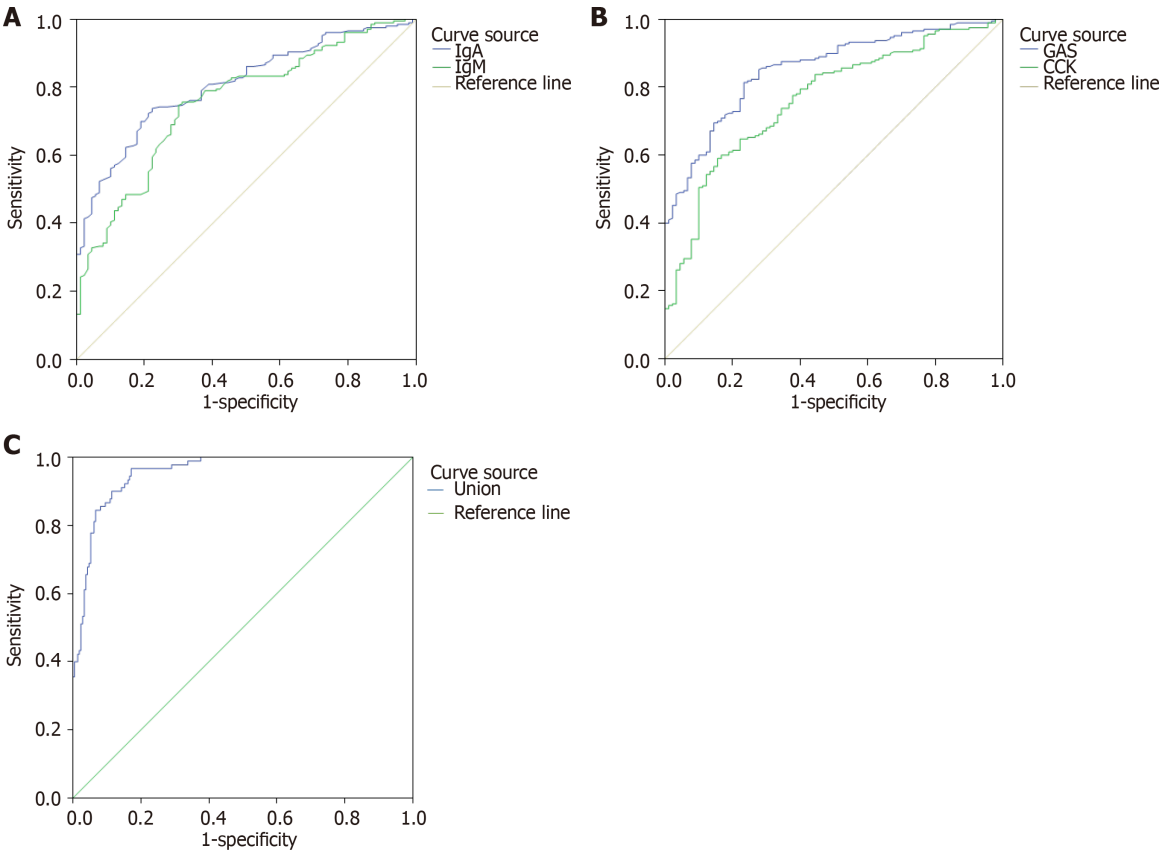

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Figure 2 The receiver operating characteristic curves. A: The receiver operating characteristic (ROC) curves for the predicted immune function; B: ROC curves predicted by gastrointestinal hormone; C: ROC curves of combined prediction, union: Immune function (immunoglobulin A and immunoglobulin M) combined with gastrointestinal hormone levels (gastrin and cholecystokinin). IgA: Immunoglobulin A; IgM: Immunoglobulin M; GAS: Gastrin; CCK: Cholecystokinin.

uncoordinated gastrointestinal motility, causing a series of complex syndromes such as fullness, belching, and abdominal pain[21]. There was no significant difference in gender, age, BMI, abdominal distension, abdominal pain, belching, nausea, vomiting and sleep disorders between the moderate-to-severe group and the mild-to-moderate group in this study, this result may be related to the sample size included in this study. However, these syndromes must be considered clinically.

Immunoglobulin is produced by B lymphocytes as long as it is a specific binding antigen. Serum IgA, IgM, and IgG are important components of the body's immune cell molecules, which can be consumed in large amounts in consumptive diseases, acute inflammation, and malignant tumors, resulting in a decline in immune function[22]. In this study, serum IgA and IgM levels in the moderate and heavy groups were lower than those in the mild and moderate groups, indicating that impaired B cell function and low immune function could aggravate the risk of infection, GU progression, and depression status. According to modern immunology, the clinical manifestations and prognosis of diseases are closely related to the functional status of T lymphocytes[23]. The percentage of serum $CD4^+$ and $CD8^+$ cells and the $CD4^+/CD8^+$ ratio reflect the cellular immune function of the body. The percentage of serum $CD4^+$ cells are helper T lymphocytes, the percentage of serum $CD8^+$ cells are inhibitory T lymphocytes, and the $CD4^+/CD8^+$ ratio is an index to assess immunity, which can reflect the immune status of the body. When the body is stimulated or damaged by stress, the percentage of $CD4^+$ cells decreased rapidly, the percentage of $CD8^+$ cells increased rapidly, the $CD4^+/CD8^+$ cell ratio increased significantly, and the immune function of the body decreases[24]. In this study, serum $CD4^+$ and $CD4^+/CD8^+$ ratios were significantly decreased in the moderate-to-heavy group, and serum $CD8^+$ levels were markedly increased. This indicates that impaired T-cell function may directly lead to the development of depression. Therefore, enhancing immune cell function is of great clinical value for controlling illness progression in patients with GU and depression.

The gastrointestinal hormone level is a sensitive index that reflects the function of the gastric mucosa. It plays an important role in regulating the function of the digestive system and is closely related to digestive system dysfunction [25]. GAS is the main hormone of the digestive tract that affects gastrointestinal transitional compound movement, prolongs gastric emptying time, stimulates the vagus nerve inhibitory fiber, promotes gastric fundus relaxation, and inhibits reflux of bile discharge[26]. When patients with GU are complicated with depression, the patient's body is in an emergency state, and the levels of stress hormones, such as hypothalamus-pituitary-adrenaline, increase, which affects the interaction between the gastrointestinal flora and gastrointestinal mucosa and the shedding of mucosal mast cells, resulting in dyspepsia[27]. In this study, the levels of serum GAS and CCK were markedly increased in the severe group. This shows that increased secretion or synthesis of gastrointestinal hormones occurs in GU patients with severe depression, leading to an imbalance in the gastrointestinal hormone balance. The low levels of GAS and CCK in plasma

affect the normal functioning of their physiological functions and slow down gastrointestinal motility, thus affecting the digestive tract symptoms of patients with depression. CCK is an important hormone that regulates the gallbladder function. Its main functions include promoting bile secretion, destroying the mucosa lining of the digestive tract, preventing gastrointestinal peristalsis, and prolonging gastric emptying[28]. The increase in CCK levels stimulates the hypothalamus and acts on the central nervous system to inhibit appetite, which is also the reason for the loss of appetite in patients with GU and depression.

In this study, the ROC curves of immune function, gastrointestinal hormone levels, and the combined prediction curve of GU and depression severity were drawn. The results showed that the immune function and gastrointestinal hormone indices alone predicted low AUC, specificity, and sensitivity, and the combined prediction had the highest efficacy, indicating that the immune function indices (IgA and IgM) combined with gastrointestinal hormone levels (GAS and CCK) have good efficacy and significance in predicting the severity of GU and depression. Serum IgA, IgM, GAS, and CCK indicators are simple, convenient, economical, effective, and have strong applicability and operability, which is conducive to the development of primary medical institutions.

Limitations of this study: All the selected participants were admitted to our hospital, the reliability may be affected by the limitation of sample size. In the later stages, the sample size can be expanded clinically, a multicenter study can be conducted, and the mechanism of immune function and gastrointestinal hormone levels in GU complicated with depression can be analyzed in depth.

CONCLUSION

In summary, the important influencing factors of GU with depression were serum IgA, IgM, GAS, and CCK indices. Immune function and gastrointestinal hormone levels can be used as effective indicators to predict the severity of GU combined with depression. Clinically, targeted measures should be taken to address these causes and reduce the risk of GU concomitant with depression.

ARTICLE HIGHLIGHTS

Research background

Psychophysiological factors play a significant role in the pathogenesis of gastrointestinal illnesses. Gastric ulcers (GU) are characterized by repeated attacks that can cause adverse severe psychological states. Some patients also experience anxiety and depression due to a lack of timely and effective treatment for physical diseases, which makes depression increasingly prominent in patients with GU.

Research motivation

The relevant risk factors and pathogenesis of GU concomitant with depression have not yet been fully elucidated. The occurrence and severity of GU complicated with depression may be related to autoimmune dysfunction and gastrointestinal hormonal disorders.

Research objectives

This study aimed to investigate the immune function, gastrointestinal hormone levels, and clinical significance of patients with GU combined with depression and to control disease progression in patients with GU complicated with depression.

Research methods

This study used a retrospective approach to analyze two indexes of immune function and gastrointestinal hormones. Furthermore, it explored the factors influencing the severity of GU concurrent depression using multivariate logistic regression analysis.

Research results

Serum immunoglobulin A (IgA), IgM, gastrin (GAS), and cholecystokinin (CCK) levels were the influencing factors affecting the severity of GU combined with depression; the area under the receiver operating characteristic curve of immune function (IgA, IgM) and gastrointestinal hormone levels (GAS, CCK) for the prediction of GU with depression severity was 0.958 (95% confidence interval: 0.933-0.976).

Research conclusions

The occurrence of GU complicated with depression is related to autoimmune dysfunction and disorders of gastrointestinal hormone levels. Immune function and gastrointestinal hormone levels can be used as effective indicators to predict the severity of GU complicated with depression.

Research perspectives

Using a retrospective analysis approach, patients were divided into severe and mild-moderate groups according to the Hamilton Depression Scale. Basic data from both groups, including immune function and gastrointestinal hormone

markers, were used to analyze the factors affecting the severity of GU and concurrent depression. To explore the value of immune function indices, gastrointestinal hormone indices and a combination of indices were used to predict the severity of GU and depression.

FOOTNOTES

Author contributions: Yang YH and Cui DJ co-designed the study, wrote the paper, contributed equally to this work, and are the first co-authors; Yang ZL, Yuan WQ, and Huang B participated in the study and provided clinical recommendations.

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ORIGINAL ARTICLE

Observational Study

Factors influencing spiritual wellbeing among pancreatic ductal adenocarcinoma patients receiving chemotherapy

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Abstract

BACKGROUND

Spiritual wellbeing emphasizes optimistic and positive attitudes while self-regulating negative emotions when coping with stress. However, there have only been a few small studies of spiritual wellbeing of pancreatic ductal adenocarcinoma (PDAC) patients undergoing chemotherapy. The core factors influencing spiritual wellbeing in this clinical population are still unclear.

AIM

To identify factors influencing spiritual wellbeing among patients with PDAC receiving chemotherapy.

METHODS

A total of 143 PDAC patients receiving chemotherapy were enrolled from January to December 2022. Patients completed general information questionnaires including: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale (FACIT-Sp-12), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Zung's Self-rating Anxiety Scale (SAS). Independent sample *t*-test, one-way analysis of variance, Pearson's correlation analysis, and multiple linear regression analysis were adopted for statistical analyses. $P < 0.05$ (two-tailed) was considered statistically significant for all tests.

RESULTS

Total spiritual wellbeing (FACIT-Sp-12) score was 32.16 ± 10.06 points, while dimension sub-scores were 10.85 ± 3.76 for faith, 10.55 ± 3.42 for meaning, and 10.76 ± 4.00 for peace. Total spiritual wellbeing score was negatively correlated with SAS score for anxiety and with the symptom domain of EORTC QLC-C30. Conversely, spiritual wellbeing score was positively correlated with global health status and EORTC QLQ-C30 role functioning domain score. Multivariate

regression analysis identified educational level, health insurance category, symptom domain, functional role domain, and global health status as significant independent factors influencing spiritual wellbeing among PDAC patients undergoing chemotherapy (R^2 = 0.502, P < 0.05).

CONCLUSION
Individualized spiritual support is needed for PDAC patients. Health, daily functioning, emotional, cognitive, and social function status should be taken into account to promote implementation of spirituality in nursing practice.

Key Words: Pancreatic ductal adenocarcinoma; Chemotherapy; Spiritual wellbeing; Quality of life; Anxiety

Core Tip: Identifying the core factors influencing spiritual wellbeing of pancreatic ductal adenocarcinoma (PDAC) patients undergoing chemotherapy and formulating individualized spiritual care regimens can improve quality of life. However, there have only been a few small studies on spiritual wellbeing of PDAC patients undergoing chemotherapy. The core factors influencing spiritual wellbeing in this clinical population are still unclear. In this study, we analyzed factors influencing the spiritual wellbeing of PDAC patients undergoing chemotherapy, the newest study of PDAC patients undergoing chemotherapy in Mainland China.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a tumor of the digestive tract with a high degree of malignancy, poor prognosis, and high mortality rate[1]. In recent years, the application of surgery combined with neoadjuvant chemotherapy has prolonged the survival of PDAC patients. However, PDAC patients undergoing chemotherapy experience surgical and chemotherapy-induced adverse events, negative emotions, changes in family and social relationships, and high treatment expenses; all of which can negatively influence health outcomes[2]. As an important part of human health, spiritual wellbeing emphasizes the role of maintaining optimistic and positive attitudes while self-regulating negative emotions when coping with stressful events. Studies have shown that spiritual wellbeing is positively correlated with health and contributes to better prognosis and quality of life[3,4]. Therefore, identifying the core factors influencing spiritual wellbeing of PDAC patients undergoing chemotherapy and formulating individualized spiritual care regimens can improve quality of life among this patient group. However, there have only been a few small studies of the spiritual wellbeing of PDAC patients undergoing chemotherapy. The core factors influencing spiritual wellbeing in this clinical population are still unclear[5,6]. Therefore, this study was designed to identify factors influencing the spiritual wellbeing of PDAC patients undergoing chemotherapy to provide a theoretical basis for formulating individualized spiritual care regimens.

MATERIALS AND METHODS

Sample size calculation

According to the sample size estimation method in *Nursing Research Methods*[7], sample size should be 5–10 times the number of independent variables. Twenty-two independent variables were included in this study, and a nonresponse rate of 10% was considered as the upper limit. According to the formula, n = 22 × (5-10) × (1+10%), the sample size should range from 121 to 242.

Patient characteristics

PDAC patients receiving cyclic adjuvant chemotherapy in our department from January 2022 to December 2022 were recruited, and 147 questionnaires were distributed and collected with a recovery rate of 100%. After four invalid questionnaires were excluded, 143 were finally included in this study with an effective recovery rate of 97.28% (Figure 1). Inclusion criteria were: (1) Diagnosis of PDAC; (2) classified as locally progressive stage disease; (3) age 18–75 years; (4) requiring cyclic chemotherapy; and (5) clearly expressed willingness to participate in the study. Exclusion criteria were: (1) Mental illness or cognitive dysfunction; and (2) insufficient energy or physical strength to complete the questionnaire.

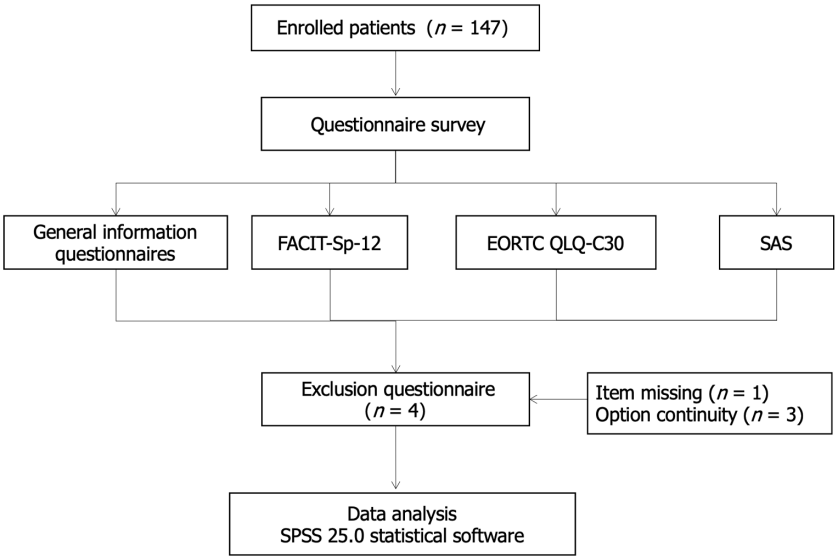

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Figure 1 Flowchart of the study design. FACIT-Sp-12: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale; SAS: Zung's Self-rating Anxiety Scale; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

Study tools

General information questionnaire: A self-designed questionnaire was distributed with items on gender, age, educational level, occupation, family income, marital status, religious beliefs, number of children, medical expenses, date of disease diagnosis, and recurrence of the disease.

Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale (FACIT-Sp-12): Spiritual well-being was measured by the FACIT-Sp-12 originally formulated by Brady *et al*[8] and translated into Mandarin by Liu *et al* [9]. Each item was scored on a 5-point Likert scale and assessed on three dimensions: faith, meaning, and peace, with higher scores indicating greater spiritual wellbeing. The Cronbach's α coefficient ranged from 0.711 to 0.920 with high validity, indicating that the FACIT-Sp-12 can be widely applied among cancer patients for the assessment of spiritual wellbeing.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30): The EORTC QLQ-C30 was a standard questionnaire designed for cancer patients by EORTC. It consisted of 30 items assessing eight quality of life dimensions. Items 29 and 30 were divided into seven levels, and scores ranged from 1 to 7 points, while all other items were scored on a 4-point Likert scale. For the functional and global health status domains, higher scores were indicative of better quality of life. For the symptom domain, a higher score indicated worse quality of life. The reliability of EORTC QLQ-C30 was 0.988 and validity was 0.989[10].

Zung's Self-rating Anxiety Scale (SAS): The SAS was designed by William W.K. Zung to reflect the degree of anxiety among patients. All items were graded on a 4-point Likert scale. A score < 50 was considered indicative of little or no anxiety, 50–60 of mild anxiety, 61–70 of moderate anxiety, and > 70 of severe anxiety[11].

Data collection methods

Prior to the survey, all investigators received standardized training to guarantee the objectivity and accuracy of data collection. All scales were completed by scanning QR codes. During the survey, investigators explained the response method and precautions for each scale by unified instructions. Each section of the questionnaire was completed by the patients independently or with the assistance of investigators. Investigators addressed any questions from patients to ensure the efficiency of questionnaire completion. After the survey, investigators examined whether any item was missing and instructed the patients to supply the missing response. Each scale required < 10 min to complete.

Statistical analysis

All data were analyzed using SPSS version 25.0 software. Quantitative data were expressed as frequency and percentage, and qualitative data as mean ± SD if it was under normal distribution. Total questionnaire scores and domain scores were compared among subgroups using the independent samples *t*-test or one-way analysis of variance (ANOVA) as indicated. Associations among total scores and domain were first assessed using Pearson's correlation analysis. Potential factors influencing spiritual wellbeing were then included in a multiple logistic regression model. A $P < 0.05$ (two-tailed) was considered statistically significant for all tests.

RESULTS

Questionnaire results

The total score of FACIT-Sp-12 of PDAC patients treated with chemotherapy was (32.16 ± 10.06), (10.85 ± 3.76) for the dimension of faith, (10.55 ± 3.42) for meaning and (10.76 ± 4.00) for peace, respectively. The SAS score was calculated as (45.59 ± 6.44). The EORTC QLQ-C30 score was (83.74 ± 2.85), (74.01 ± 21.41) for global health status and (8.88 ± 1.79) for the symptom domain. The results of all questionnaires are summarized in Table 1.

Differences in spiritual wellbeing among demographic and clinical subgroups

Significant differences were observed in the spiritual wellbeing regarding sex, education level, household monthly income, type of health insurance and recurrence of PDAC patients treated with chemotherapy. Spiritual wellbeing scores were higher in males than females, in higher-educated compared to less-educated patients, and in patients at first diagnosis (without recurrence) (all $P < 0.05$), but showed no significant difference among age group, duration of illness, or occupational group (Table 2). Further, scores also differed by household monthly income and type of health insurance (both $P < 0.05$). The spiritual wellbeing score of patients with a household monthly income of 3000–5000 Yuan was the highest up to (35.00 ± 8.64), and the lowest score was (29.37 ± 10.65) in their counterparts with income of 1000–3000 Yuan. Patients with workers' medical insurance had the highest spiritual wellbeing score of 35.68 ± 7.80, and those with other types of health insurance obtained the lowest score of 19.42 ± 11.87.

Associations of spiritual wellbeing with anxiety and quality of life

The correlation coefficients between spiritual wellbeing and anxiety, and symptom domain of EORTC QLQ-C30 were calculated as -0.357 and -0.322, and those between spiritual wellbeing and global health status, and function domain were 0.464 and 0.421 ($P < 0.05$). These findings suggested that spiritual wellbeing was negatively correlated with anxiety level as measured by the SAS score and with the quality of life symptom domain according to EORTC QLQ-C30. The high spiritual wellbeing was predictive of lower anxiety and better symptom-related quality of life. Conversely, heightened anxiety and severity of symptoms were associated with lower spiritual wellbeing. In addition, spiritual wellbeing was positively correlated with global health status and the functional role domain of quality of life (all $P < 0.05$) (Table 3).

Independent factors predictive of spiritual wellbeing

In multivariate regression analysis, FACIT-Sp-12 total score was considered the dependent variable and all variables significantly associated with the wellbeing score in ANOVA (anxiety, functional role domain of EORTC QLQ-C30, global health status, and symptom domain) were included as independent variables (default values are shown in Table 4). Educational level, type of health insurance, functional role domain of the EORTC QLQ-C30, symptom domain of the EORTC QLQ-30, and global health status of the EORTC QLQ-30 were identified as independent factors influencing spiritual wellbeing (overall $R^2 = 0.502$, $P < 0.05$) (Table 5).

DISCUSSION

Spiritual wellbeing of PDAC patients treated with chemotherapy needs to be enhanced. The total spiritual wellbeing score for patients with PDAC undergoing chemotherapy was in the mid-range (32.16 ± 10.06), consistent with other patient populations described by Xue *et al*[12] and Liu *et al*[13], and indicating the need for improvement through spiritual care regimens. The diagnosis of PDAC places heavy emotional and financial burdens on patients[14]. Although surgery combined with neoadjuvant chemotherapy can prolong survival[15], the overall survival rate is still low[16], which increases uncertainty about life and reduces patient confidence in treatment outcome. Cyclic chemotherapy is a substantial imposition, disrupting lifestyle and social participation, with side effects including physical pain and other discomforts that further increase the psychological burden[13], which may eventually lower spiritual wellbeing. Therefore, medical staff should actively provide spiritual support, identify patients' negative emotions, strengthen health education, emphasize the importance of companionship, and create a positive atmosphere. Potential strategies included sharing treatment success stories, encouraging patients to reflect on the meaning of life, and alleviating negative emotion to help the patient achieve harmony of body, heart, and spirit.

Individual differences in spiritual wellbeing were related to demographics and clinical status. Although PDAC incidence was lower in females than males, the former reported significantly lower spiritual wellbeing, possibly due to a greater propensity for negative emotions in response to stressful events[17,18]. However, at present, the causes of gender difference on spiritual wellbeing are still unclear and warrant further investigation to formulate gender-specific spiritual care regimens for PDAC patients undergoing chemotherapy. Patients with higher educational level reported greater spiritual wellbeing. Many of these patients also reported a heavy economic burden (76%), which may explain why spiritual wellbeing was higher among PDAC patients in households with a monthly income of 3000–5000 Yuan compared to those with income of 1000–3000 Yuan. However, several studies[19-21] have found that household income was not an influencing factor on the spiritual wellbeing of cancer patients. Patients with higher household monthly incomes and urban medical insurance experience less pressure from medical expenses and were able to afford better chemotherapy; therefore, this group of patients could maintain a better quality of life. Nonetheless, the subgroup of patients with monthly income > 5000 Yuan did not have significant additional benefits, possibly due to the small sample size. Recurrence of PDAC was also an influencing factor for spiritual wellbeing as recurrence can intensify uncertainty and

Table 1 Questionnaire results for pancreatic ductal adenocarcinoma patients treated with chemotherapy (*n* = 143)

Item	Score range	Scale score	mean item score
FACIT-Sp-12	0-48	32.16 ± 10.06	2.68 ± 0.84
Faith	0-16	10.85 ± 3.76	2.71 ± 0.94
Meaning	0-16	10.55 ± 3.42	2.64 ± 0.86
Peace	0-16	10.76 ± 4.00	2.69 ± 1.00
SAS	0-100	45.59 ± 6.44	2.28 ± 0.32
Anxiety	0-20	5.48 ± 1.96	1.37 ± 0.49
Vegetative disorder	0-40	11.01 ± 2.90	1.38 ± 0.36
Exercise-induced anxiety	0-30	15.43 ± 2.40	2.57 ± 0.40
Concurrent symptoms of anxiety and vegetative disorder	0-10	4.54 ± 1.27	2.27 ± 0.64
EORTC QLQ-C30	0-100	83.74 ± 2.85	5.58 ± 0.19
Body	0-100	18.46 ± 15.52	3.69 ± 3.10
Role functioning	0-100	16.32 ± 19.33	8.16 ± 9.67
Emotion	0-100	14.74 ± 18.65	3.69 ± 4.67
Cognition	0-100	19.35 ± 19.74	9.67 ± 9.87
Social function	0-100	28.79 ± 24.80	14.39 ± 12.40
QLQ-C30 global health status	0-100	74.01 ± 21.41	37.00 ± 10.70
QLQ-C30 symptom domain	0-11	8.88 ± 1.79	0.68 ± 0.14
Fatigue	0-100	75.76 ± 21.04	25.25 ± 7.01
Nausea and vomiting	0-100	89.04 ± 17.48	44.52 ± 8.74
Pain	0-100	82.63 ± 21.29	41.32 ± 10.65
Shortness of breath	0-100	85.32 ± 21.89	
Insomnia	0-100	76.46 ± 27.07	
Loss of appetite	0-100	76.22 ± 27.59	
Constipation	0-100	86.71 ± 20.98	
Diarrhea	0-100	86.71 ± 20.98	
Economic difficulty	0-100	85.55 ± 25.50	

FACIT-Sp-12: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale; SAS: Zung's Self-rating Anxiety Scale; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

reduce individual capacity to resolve difficulties, thereby lowering spiritual wellbeing. Medical staff should act to address issues such as economic pressure, negative emotions, and poor knowledge of treatment benefits and challenges, especially among female patients, to improve spiritual wellbeing.

In this study, the mean SAS score was in the very low range, albeit higher than reported previously[5] and was negatively correlated with spiritual wellbeing. Symptoms such as dyspnea (83.91%), irritation (78.32%), fatigue (51.05%), poor sleep (48.25%), and gastrointestinal reactions (46.15%) can induce anxiety. Long-term anxiety among these patients may evoke hypersensitivity to negative events, causing loss of faith in the treatment process, reducing optimism, and even leading to suicide[22,23]. Therefore, medical staff should closely monitor and attempt to mitigate anxiety by regulating respiratory and gastrointestinal functions, improving sleep and psychological state, encouraging patients to express their true emotions, mentally preparing patients to face negative events with a peaceful attitude, and strengthening their optimism.

High quality of life related to functional role and global health status can enhance spiritual wellbeing. In contrast, the functional role domain score and global health status score were predictive of greater spiritual wellbeing. More than 60% of these patient were unable to perform persistent physical activities due to advanced stage disease[24], which can interfere with family life and social activities, thereby provoking negative emotions. The difficulties in long cycles of treatment and the unpredictable health outcome may cause substantial anxiety, leading to negative emotions, reluctance to communicate with others, and ultimately loss of faith and meaning in life. Patients with high social support were more inclined to welcome alternative opinions and enjoy the companionship of others to relieve stress, find peace of mind, and

Table 2 Differences in spiritual wellbeing among demographic and clinical subgroups of pancreatic ductal adenocarcinoma patients on chemotherapy (*n* = 143)

Item		No. of cases, *n* (%)	Spiritual wellbeing score	*T*/*F*	*P* value
Sex	Male	93 (65.0)	32.89 ± 10.54	1.187	0.024
	Female	50 (35.0)	30.80 ± 9.06		
Age (yr)	18–44	18 (12.6)	29.67 ± 10.32	0.495[1]	0.687
	45–59	79 (55.2)	32.39 ± 10.16		
	60–74	36 (25.2)	32.39 ± 10.52		
	75–89	10 (7.0)	32.16 ± 10.06		
Education level	Primary school or below	37 (25.9)	26.03 ± 10.48	12.399[1]	< 0.001
	Middle and high school	62 (43.4)	32.19 ± 9.33		
	Technical and further education	20 (14.0)	33.6 ± 7.00		
	Undergraduate degree or above	24 (16.8)	40.33 ± 7.10		
Occupation	Farmer	73 (51.0)	32.49 ± 10.55	1.047[1]	0.374
	Retired	34 (23.8)	32.21 ± 10.23		
	Full-time employment	20 (14.0)	28.90 ± 9.99		
	Other	16 (11.2)	34.63 ± 6.86		
Household monthly income	> 1000 Yuan	35 (24.5)	31.03 ± 11.09	2.685[1]	0.049
	1000–3000 Yuan	30 (21.0)	29.37 ± 10.65		
	3000-5000 Yuan	56 (39.2)	35 ± 8.64		
	5000 Yuan plus	22 (15.4)	30.55 ± 9.80		
Spouse	Yes	124 (86.7)	31.59 ± 10.05	-1.749	0.082
	No	19 (13.3)	35.89 ± 9.57		
Religious belief	Yes	3 (2.1)	35 ± 14.73	0.493	0.623
	No	140 (97.9)	32.1 ± 10.01		
Number of offspring	0	4 (2.8)	39 ± 4.24	1.654[1]	0.180
	1	65 (45.5)	33.42 ± 9.37		
	2	58 (40.6)	31.10 ± 10.37		
	3 or more	16 (11.2)	29.19 ± 11.77		
Type of health insurance	Employee Health Insurance	62 (43.4)	35.68 ± 7.80	11.282[1]	< 0.001
	New rural pension scheme	63 (44.1)	30.98 ± 9.65		
	Urban medical insurance	6 (4.2)	33.67 ± 10.35		
	Other	12 (8.4)	19.42 ± 11.87		
Time after diagnosis	≤ 6 mo	69 (48.3)	33.42 ± 8.44	1.278[1]	0.284
	7–12 mo	40 (28.0)	30.95 ± 11.11		
	13–24 months	17 (11.9)	28.76 ± 13.26		
	≥ 24 mo	17 (11.9)	33.29 ± 9.76		
Recurrence	Yes	28 (19.6)	26.18 ± 12.19	-3.035	< 0.001
	No	115 (80.4)	32.16 ± 10.06		

[1]*F* test.

Table 3 Correlations among spiritual wellbeing, anxiety, and quality of life scores (*n* = 143)

Item	Spiritual wellbeing	Faith	Meaning	Peace
SAS	-0.357[b]	-0.329[b]	-0.345[b]	-0.293[b]
Anxiety	-0.371[b]	-0.366[b]	-0.319[b]	-0.316[b]
Vegetative disorder	-0.466[b]	-0.420[b]	-0.469[b]	-0.378[b]
Exercise-induced anxiety	0.053	0.067	0.047	0.030
Concurrent symptoms of anxiety and vegetative disorder	0.092	0.061	0.079	0.106
EORTC QLQ-C30	0.421[b]	0.381[b]	0.437[b]	0.329[b]
Body	0.292[b]	0.302[b]	0.266[b]	0.225[b]
Role functioning	0.181[a]	0.177[a]	0.223[b]	0.100
Emotion	0.436[b]	0.387[b]	0.436[b]	0.362[b]
Cognition	0.324[b]	0.275[b]	0.335[b]	0.271[b]
Social function	0.301[b]	0.229[b]	0.368[b]	0.229[b]
QLQ-C30 global health status	0.464[b]	0.362[b]	0.435[b]	0.456[b]
QLQ-C30 symptom domain	-0.322[b]	-0.320[b]	-0.331[b]	-0.226[b]
Fatigue	-0.264[b]	-0.294[b]	-0.245[b]	-0.177[a]
Nausea and vomiting	-0.169[a]	-0.210[a]	-0.144	-0.105
Pain	-0.275[b]	-0.278[b]	-0.294[b]	-0.180[a]
Shortness of breath	-0.214[a]	-0.231[b]	-0.183[a]	-0.166[a]
Insomnia	-0.281[b]	-0.229[b]	-0.302[b]	-0.234[b]
Loss of appetite	-0.309[b]	-0.295[b]	-0.323[b]	-0.225[b]
Constipation	-0.189[a]	-0.213[a]	-0.183[a]	-0.119
Diarrhea	-0.199[a]	-0.162	-0.242[b]	-0.143
Economic difficulty	-0.098	-0.042	-0.156	-0.074

[a]$P < 0.05$.
[b]$P < 0.01$. SAS: Zung's Self-rating Anxiety Scale; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

Table 4 Default values of independent variables for multivariable regression

Independent variable	Default value
Sex	Male = 1; female = 2
Education level	Primary school or below = 1; middle and high school = 2; technical and further education = 3; bachelor degree and above = 4
Household monthly income (Yuan)	< 1000 = 1; 1000-3000 = 2; 3000-5000 = 3; > 5000 = 4
Type of health insurance	Workers' medical insurance = 1; new rural pension scheme = 2; urban medical insurance = 3; other = 4
Recurrence	Yes = 1; No = 2

better adapt to life challenges. Therefore, medical staff should provide comprehensive and individualized spiritual care aiming to assist and encourage patients to positively accept and face negative events through disease cognition, psychological counseling, and life review.

The symptom domain of quality of life negatively affects spiritual wellbeing, suggesting that severe symptoms and concomitant poor quality of life can degrade spiritual wellbeing. This was consistent with the findings of Du *et al*[25], who also found that most PDAC patients treated with chemotherapy developed symptoms such as fatigue (68%) and insomnia (52%), which may have persisted during the course of treatment[26]. Patients with chronic fatigue were prone to express negative emotions, while discomfort from cyclic chemotherapy and chronic disease pain aggravated insomnia and lowered life expectations[27,28]. Consequently, medical staff should closely monitor adverse symptoms such as

Table 5 Multiple linear regression analysis of factors independently influencing spiritual wellbeing (*n* = 143)

Item	FACIT-Sp-12				
	b	sb	b'	*t* value	*P* value
(Constant)	-74.696	42.693	-	-1.750	0.082
Sex	0.518	1.397	0.025	0.371	0.711
Education level	3.297	0.639	0.332	5.156	< 0.001
Household monthly income	0.013	0.65	0.001	0.020	0.984
Type of health insurance	-3.02	0.798	-0.263	-3.786	< 0.001
recurrence	2.198	1.739	0.087	1.264	0.209
SAS anxiety	-0.214	0.12	-0.137	-1.786	0.076
C30 global health status	0.988	0.416	0.279	2.371	0.019
C30 symptom domain	0.152	0.037	0.323	4.117	< 0.001
C30 functional domain	1.647	0.643	0.293	2.559	0.012

F = 14.902, P = 0.000, R = 0.709, R^2 = 0.502. FACIT-Sp-12: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale.

fatigue and insomnia to alleviate discomfort and improve life expectations, possibly *via* family guidance and mindfulness meditation.

This study had several limitations. Most patients were from southwestern China (Chongqing) and so this may not be a nationally representative sample. Future studies will expand the sample size and evaluate the effects of specific religious beliefs on the spiritual wellbeing of PDAC patients receiving chemotherapy.

CONCLUSION

Education level, health insurance category, symptom domain, functional role domain and global health status were the main factors influencing spiritual wellbeing among PDAC patients undergoing chemotherapy. Individualized spiritual care regimens can be formulated through life care, behavioral therapy, mindfulness meditation, cognitive interview, and life review among other strategies.

ARTICLE HIGHLIGHTS

Research background

Identifying the core factors influencing spiritual wellbeing of pancreatic ductal adenocarcinoma (PDAC) patients undergoing chemotherapy and formulating individualized spiritual care regimens can improve quality of life among this patient group. However, there have only been a few small studies of the spiritual wellbeing of PDAC patients undergoing chemotherapy. The core factors influencing spiritual wellbeing in this clinical population are still unclear. Therefore, this study was designed to identify factors influencing the spiritual wellbeing of PDAC patients undergoing chemotherapy.

Research motivation

This study was designed to investigated the spiritual wellbeing status and identify factors influencing the spiritual wellbeing of PDAC patients undergoing chemotherapy. To draw attention to the spiritual health of patients with pancreatic cancer undergoing chemotherapy and formulate individualized spiritual care regimens.

Research objectives

This study was designed to investigated the spiritual wellbeing status and identify factors influencing the spiritual wellbeing of PDAC patients undergoing chemotherapy. This study found that effective measures to mitigate anxiety and increase quality-of-life-related role functioning, emotional guidance, cognition of disease, social function, and life education may enhance spiritual wellbeing. Individualized spiritual care regimens can be formulated through life care, behavioral therapy, mindfulness meditation, cognitive interview, and life review among other strategies.

Research methods

The research method of this study was a questionnaire survey. Prior to the questionnaire survey, all investigators received standardized training to guarantee the objectivity and accuracy of data collection. The questionnaire included a

general information questionnaire, Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Zung's Self-rating Anxiety Scale. All data were analyzed using SPSS version 25.0. $P < 0.05$ (two-tailed) was considered statistically significant for all tests.

Research results

This study investigated the spiritual wellbeing of Chinese patients with PDAC undergoing chemotherapy and analyzed its influencing factors for the first time. This study found that individualized spiritual care regimens can be formulated through life care, behavioral therapy, mindfulness meditation, cognitive interview, and life review among other strategies. This study had limitations. Most patients were from southwestern China (Chongqing), so this may not be a nationally representative sample. Future studies will expand the sample size and evaluate the effects of specific religious beliefs on the spiritual wellbeing of PDAC patients receiving chemotherapy.

Research conclusions

Spiritual wellbeing of PDAC patients treated with chemotherapy was in the mid-range, and individual differences in spiritual wellbeing related to demographics and clinical status. Anxiety and symptom severity markedly disrupted the spiritual wellbeing of PDAC patients undergoing chemotherapy, whereas a sustained functional role and good global health status related to quality of life promoted spiritual wellbeing. This study provides a theoretical basis for formulating individualized spiritual care regimens.

Research perspectives

Future studies will expand the sample size and evaluate the effects of specific religious beliefs on the spiritual wellbeing of PDAC patients receiving chemotherapy.

FOOTNOTES

Author contributions: Wei LL, Zhang ST contributed to the conception and design of the study; Wei LL and Zhang ST contributed equally to this work as joint first authors; Mi N contributed to the administrative support; Liao Y contributed to the provision of study materials or patients; Zhang ST, Liao Y, Zhang Y, Yu Y collected and analyzed the data; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Organized physical activity and sedentary behaviors in children and adolescents with autism spectrum disorder, cerebral palsy, and intellectual disability

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Abstract

BACKGROUND

There is little data on physical activity (PA), organized PA (OPA), and sedentary behaviors in autism spectrum disorders (ASD) and other neurodevelopmental disorders in developing countries.

AIM

To examine OPA, non-OPA, and sedentary behaviors and their associated factors in children and adolescents with ASD, cerebral palsy (CP), and intellectual disability (ID).

METHODS

A total of 1020 children and adolescents with ASD, CP, and ID were assessed regarding the child and family information as well as the Children's Leisure Activities Study Survey.

RESULTS

The results showed that the OPA level was significantly lower than non-OPA in all groups. Furthermore, the OPA level was significantly lower in the CP group compared to ASD and ID groups ($P < 0.001$). Also, moderate ($P < 0.001$), vigorous ($P < 0.05$), and total ($P < 0.001$) physical activity levels were significantly different between all three groups, with the values being higher in the ASD group

compared to the other two. The mean of the total sedentary behavior duration in the ASD group (1819.4 min/week, SD: 1680) was significantly lower than in the CP group (2687 min/week, SD: 2673) (P = 0.007) but not ID group (2176 min/week, SD: 2168.9) (P = 0.525).

CONCLUSION

Our findings remark on the participation rate of PA, OPA, and sedentary behaviors of children and adolescents with ASD, CP, and ID in a developing country. In contrast, the need for developing standards of PA/OPA participation in neurodevelopmental disorders is discussed.

Key Words: Neurodevelopmental disorders; Physical disability; Mental disability; Active lifestyle

Core Tip: There is little data on physical activity (PA), organized PA (OPA), and sedentary behaviors in autism spectrum disorder (ASD) and in developing countries. A total of 1020 children and adolescents with ASD, cerebral palsy (CP), and intellectual disability (ID) were assessed regarding their physical activity. Our findings remark on the participation rate of PA, OPA, and sedentary behaviors of children and adolescents with ASD, CP, and ID in a developing country.

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INTRODUCTION

Sedentary behavior has been defined as any waking behavior with an energy expenditure ≤ 1.5 metabolic equivalents while in a sitting, reclining, or lying posture and is associated with chronic underlying diseases such as diabetes and cardiovascular diseases[1-3]. On the other hand, non-organized physical activity (PA) is defined as any bodily movement that requires energy expenditure higher than sedentary behavior level, and organized PA (OPA) is defined as involving in regular and structured health and leisure activities with peers, coaches, and group leaders such as tennis, football, etc [4].

Plenty of literature points to the importance of PA in children; however, levels of PA are insufficient for different groups of children, particularly those with disabilities[5]. The optimal level of PA can increase health status and decrease the incidence of chronic disorders such as cancer, diabetes, cardiovascular disorders, and mood disorders[6]. Mental, intellectual, and motor disabilities negatively impact the opportunities to participate in an optimal level of PA to gain health benefits and limit sedentary behaviors consequences[7]. In other words, children with particular disabilities, such as neurodevelopmental disorders, may be limited regarding motor disabilities and social skills[8]. For example, children with autism spectrum disorders (ASD) participate in less PA[9] and more sedentary behaviors than their peers leading to greater body mass index (BMI) in comparison to typically developing (TD) children[10-12]. In addition, according to estimates of developed countries, children with neurodevelopmental disorders such as ASD, cerebral palsy (CP), and intellectual disability (ID) also participated less in a regular and OPA than those children without a neurodevelopment disability[13-17]. Studies have also shown children with neurodevelopmental disabilities encounter additional personal and environmental barriers that hinder their participation in physical activities compared to TD children[10,18].

Although the disability characteristics should be considered[8], participation in PA, benefiting from its psychosocial and motor advantages, is of paramount importance for children with neurodevelopmental disorders[8,19]. PA could also enhance cognitive and meta-cognitive function and improve educational performance[20-22]. Moreover, OPA provides additional benefits, including promoting inclusion, facilitating social connection, improving social and emotional well-being, and reducing functional decline[23]. For example, Sun *et al*[24], in a clinical trial, assessed the effects of an adapted PA consisting of moderate-intensity aerobic and resistance exercises on health-related physical fitness in adolescents with ID. The authors declared significant changes were observed in cardiorespiratory fitness, running/walking tests, and flexibility in the intervention group compared to the control group. In addition, in a recent systematic review and meta-analysis, Howells *et al*[23] represented that group-based OPA participation improves overall social functioning in children with ASD. Moreover, Mak *et al*[25] reported the positive effect of a regular 8-wk mindfulness yoga program on attention outcomes of children with CP. However, due to motor skill limitations, such a positive impact was not observed in their physical skills outcomes. Given the above, OPA is a constructive and helpful context in which children and adolescents with neurodevelopmental disorders could benefit from opportunities, including social engagement, promoting social skills, enhancing mental health, and improving quality of life[26,27].

Despite valuable research in terms of the effect of PA and OPA on different aspects of neurodevelopmental disorders, there are few studies assessing the rate of OPA participation in children with ASD in comparison to other neurodevelop-

mental groups and not TD children. Arim *et al*[8] assessed the PA/OPA participation rate in 4-9 years old Canadian children with neurodevelopmental disorders (including epilepsy, CP, ID, and learning disability) compared to TD children. Their results represented that although the frequency of OPA participation in this population varied depending on the child's health condition, there was no significant difference in general PA participation among different neurodevelopmental groups.

Thus, the current study aimed to assess and compare sedentary behavior, OPA, and non-OPA levels, as primary outcomes in children and adolescents with ASD, ID, and CP. We also aimed to determine the personal and familial factors associated with PA and sedentary behavior among these children. This is one of the few studies on PA levels among children with neurodevelopmental disorders in the context of a developing country, utilizing a large sample size. The findings of this study may help to identify the groups which benefit the most from the interventions to improve PA levels and can be a basis for future studies in the context of developing countries.

MATERIALS AND METHODS

Study design and setting

The data for the current cross-sectional study were drawn from a longitudinal survey of "Quality of life and psycho-physical function in children and adolescents with developmental disabilities; evaluating risk factors and developmental trend", which was conducted from 2011 to 2021 with a sample size of 1850 participants (1040 boys and 810 girls) aged 6-18 years from special schools in Tehran, Iran. Participants were included in the study by stratified random sampling. The population was stratified into different strata by disorders; each stratum was divided into different clusters (schools), respectively. Then five schools were included for each stratum (disorder). Afterward, children's parents/caregivers responded to the Children's Leisure Activities Study Survey (CLASS questionnaire) to examine the children's non-OPA (*i.e.*, general routine PA), OPA, and sedentary behavior activities. The study was approved by the ethics committee of Tehran University of medical sciences (ethics code: IR.TUMS.NI.REC.1401.031), and written consent was obtained from participants' parents/caregivers before entering the study.

Participants

Children and adolescents with neurodevelopmental disorders were included in the current study. The diagnosis of ASD was confirmed by DSM-IV, and the autism diagnostic inventory-revised by a professional child psychiatrist. The participants were excluded if they had two or three of the conditions (*i.e.*, ASD, CP, or ID) together and being less than six years of age.

Measurements

Basic and sociodemographic data: Parents/caregivers of the participants were asked to fill the items of a questionnaire containing child and family basic and sociodemographic information, including the child's age, gender, childcare status (two parents, single parent, and other), household status (owner, tenant, and other), parents' age, and parents' educational level. Physical therapists also conducted a physical examination to measure participants' height, weight, waist circumference, and hip circumference. Moreover, the existence of any musculoskeletal disorder preventing physical movements was assessed based on physical examination as well as the participants' medical history by a physical therapist.

Non-OPA/OPA and sedentary behavior data: We used the Persian version of the CLASS to assess non-OPA/OPA and sedentary behavior. This survey measures the type, frequency, and duration of different types of PA, including non-OPA and OPA as well as sedentary behavior among children. The CLASS checklist contains items for both non-OPA (such as playing indoors with toys, walking the dog, *etc.*) and OPA (such as football, basketball, aerobics, *etc.*), as well as items for sedentary behaviors (such as sitting, talking, listening to music, and reading). Previous studies have demonstrated test-retest reliability (ICC > 0.58 across different domains) and criterion validity CLASS[28].

Statistical methods

First, descriptive statistics for basic, demographic, and sociodemographic variables, PA/OPA, and sedentary behavior data were calculated for each group. We used the chi-square test to compare the categorical variables between groups. We also used the Kolmogorov-Smirnov test to test if the continuous variables are distributed normally. As none of the continuous variables had normal distribution, we used non-parametric tests, such as the Kruskal-Wallis test, to compare them between groups. Moreover, the Mann-Whitney *U* test was also conducted to compare two individual groups whenever the difference between the three groups was significant. Finally, the Wilcoxon test was used to compare OPA and non-OPA levels in all groups. All analyses were conducted using SPSS version 26, while a *P* value of less than 0.05 was considered significant.

RESULTS

Descriptive statistics

In the current study, 1020 participants (ASD: 248, CP: 306, ID: 466) were included in the final analysis (Table 1 shows the

Table 1 Basic and demographic data of participants in autism spectrum disorders, intellectual disability, and cerebral palsy groups, *n* (%)

Variables	ASD	ID	CP	*P* value
Gender; Female	9 (3.6)	247 (53.0)	160 (52.3)	**< 0.001**
Age (yr); mean (SD)	11.15 (2.7)	12.69 (3.0)	12.11 (3.2)	**< 0.001**
Height (cm); mean (SD)	145.51 (16.20)	141.55 (17.30)	137.01 (18.70)	**< 0.001**
Weight (kg); mean (SD)	44.98 (19.10)	42.70 (18.10)	38.73 (20.70)	**< 0.001**
WC (cm); mean (SD)	70.90 (13.60)	72.19 (15.10)	66.53 (11.80)	**< 0.001**
HC (cm); mean (SD)	81.16 (12.60)	82.72 (15.40)	76.23 (12.80)	**< 0.001**
WHR; mean (SD)	0.86 (0.10)	0.87 (0.20)	0.87 (0.10)	0.691
Musculoskeletal disorder	27 (10.9)	70 (15.0)	78 (25.5)	**< 0.001**
Household				
Owner	131 (55.0)	239 (54.2)	108 (37.9)	**< 0.001**
Tenant	92 (38.7)	178 (40.4)	141 (49.5)	
Other	15 (6.3)	24 (5.4)	36 (12.6)	
Childcare				
Two parents	201 (91.8)	350 (85.8)	242 (89.3)	0.157
Single parent	17 (7.8)	48 (11.8)	25 (9.2)	
Other	1 (0.5)	10 (2.5)	4 (1.5)	
Father's education				
Lower than diploma	39 (16.5)	217 (48.5)	122 (43.9)	**< 0.001**
Diploma (11 yr of education)	70 (29.5)	134 (30.0)	89 (32.0)	
Higher than diploma	128 (54.0)	96 (21.5)	67 (24.1)	
Mother's education				
Lower than diploma	37 (15.3)	215 (48.4)	105 (36.1)	**< 0.001**
Diploma (11 yr of education)	85 (35.1)	159 (35.8)	132 (45.4)	
Higher than diploma	120 (49.6)	70 (15.8)	54 (18.6)	
Father's age (yr); mean (SD)	43.98 (6.70)	46.2 (7.7)	43.2 (6.9)	**< 0.001**
Mother's age (yr); mean (SD)	38.30 (6.50)	41.2 (7.1)	38.1 (6.7)	**< 0.001**

ASD: Autism spectrum disorders; CP: Cerebral palsy; HC: Hip circumference; ID: Intellectual disability; SD: Standard deviation; WC: Waist circumference; WHR: Waist to hip ratio.

descriptive statistics). In the ASD group, 3.6% of participants were female, which is significantly lower than the ID and CP groups (53% and 52.3%, respectively; $P < 0.001$). In pairwise comparison, there were significant differences between groups regarding their ages ($P < 0.05$), with the ASD group being the youngest (mean = 11.15, SD = 2.66) and the ID group being the oldest (mean = 12.69, SD = 3.15). Similarly, height was significantly different between all three groups ($P < 0.05$). Also, children with CP had lower weights ($P < 0.01$), smaller waist circumferences ($P < 0.01$), and smaller hip circumferences ($P \leq 0.001$) than the other groups. In addition, the prevalence of musculoskeletal disorders was significantly higher in the CP group compared to both ASD and ID groups ($P < 0.001$). The parents in the ASD group were more educated than both CP and ID groups ($P < 0.001$). Parents of children with ID were significantly older than the parents of the other two groups ($P \leq 0.001$).

Non-OPA/OPA and sedentary behavior results

Table 2 presents and compares the physical activity levels of children with ASD, ID, and CP. Our results showed that the level of OPA is significantly lower in comparison to non-OPA in ASD ($P < 0.001$), CP ($P < 0.001$), and ID ($P < 0.001$) groups (Table 2). Furthermore, the OPA level was significantly lower in the CP group compared to ASD and ID groups ($P < 0.001$). Also, non-OPA levels were significantly different between the three groups ($P < 0.001$). Also, in pairwise comparisons, moderate ($P < 0.001$), vigorous ($P < 0.05$), and total ($P < 0.001$) physical activity levels were significantly different between all three groups, with the values being higher in the ASD group compared to the other two.

Table 2 The amount of physical activity/organized physical activity (minutes per week) and level of physical activity in autism spectrum disorders in comparison to control intellectual disability, and cerebral palsy groups

Min/week	ASD, mean (SD)	ID, mean (SD)	CP, mean (SD)	*P* value
OPA				
Aerobic exercise	1.0 (8.7)	1.1 (10.2)	0.6 (6.5)	0.938
Dancing	7.3 (30.7)	14.2 (44.6)	6.9 (38.3)	**< 0.001**
Gymnastic	2.2 (24)	0.6 (8.1)	0.2 (3.1)	0.367
Tennis	0.4 (3.9)	2.0 (16.9)	4.7 (51.5)	0.323
Football	10.5 (59.4)	9.2 (34.4)	3.7 (28.2)	**0.003**
Volleyball	2.6 (29.2)	1.3 (9.4)	0.4 (4.3)	0.246
Basketball	0.8 (12.1)	2.3 (26.7)	0.3 (4.2)	0.475
Handball	0 (0)	0.1 (2.5)	0.3 (3.3)	0.132
Swimming laps	11.1 (58.2)	2.6 (17.4)	1.2 (10.2)	**0.008**
Rollerblading	4.2 (24.7)	3.6 (37.7)	0.2 (2.9)	**0.017**
Skateboarding	0.7 (8.3)	0.9 (15.4)	0.3 (4.2)	0.690
Physical education class	2.3 (14.7)	1.9 (11.5)	1.1 (8.6)	0.567
Sport class at school	16.4 (25.1)	10.5 (24.9)	6.6 (17.1)	**< 0.001**
Total OPA	59.5 (134.0)	50.4 (101.3)	26.6 (85.1)	**< 0.001**
Non-OPA (mins/week)				
Bicycling	27.4 (95.7)	11.7 (49.8)	9.4 (76.6)	**< 0.001**
Scooter	6.9 (37)	4.0 (29.3)	0.5 (4.6)	**0.008**
Skipping rope	1.6 (17.2)	0.8 (5.8)	0.3 (3.6)	**0.047**
Playing with the ball	0.7 (7.9)	1.7 (29.4)	0.3 (5.1)	0.377
Tag/chasey	2.1 (20.8)	3.8 (20.8)	0.6 (7.3)	**< 0.001**
Household chores	23.5 (70.7)	26.3 (94.8)	10.6 (53)	**< 0.001**
Walk for exercise	49.7 (103.5)	23.7 (55.9)	22.7 (135.6)	**< 0.001**
Play on playground equipment	48.2 (95.7)	22.7 (53.9)	13.6 (43.5)	**< 0.001**
Jogging or running	17.4 (82.6)	9.2 (35.0)	4.1 (22.1)	**< 0.001**
Swimming for fun	21.8 (48.6)	6.6 (25.1)	9.8 (34.5)	**< 0.001**
Bounce on the trampoline	4.9 (30.1)	1.5 (15.3)	0.5 (4.9)	**< 0.001**
Play with pet	2.3 (18.6)	3.7 (24)	5.5 (41.9)	0.471
Travel to school by walking	4.0 (21.3)	6.1 (31.9)	1.2 (9.8)	**< 0.001**
Travel to school by bicycling	0.2 (3.8)	0.2 (2.4)	0.1 (2.3)	0.822
Total non-OPA	210.8 (295.3)	122.1 (210.1)	79.4 (207.5)	**< 0.001**
Level of PA/OPA				
Moderate physical activity	198.7 (277.1)	129.4 (206.9)	79.8 (207.2)	< 0.001
Vigorous physical activity	71.5 (159.4)	43.1 (111.9)	26.1 (84.2)	< 0.001
Total physical activity	270.3 (372.9)	172.4 (275.3)	105.9 (241.8)	< 0.001

PA: Physical activity; OPA: Organized physical activity; ASD: Autism spectrum disorders; CP: Cerebral palsy; ID: Intellectual disability; SD: Standard deviation.

Table 3 The amount of sedentary behavior (minutes per week) in autism spectrum disorders in comparison to control intellectual disability, and cerebral palsy groups

Variables (mins/week)	ASD, mean (SD)	ID, mean (SD)	CP, mean (SD)	*P* value
Watching TV	465.8 (628.1)	709.8 (810.0)	747.3 (788.9)	**< 0.001**
Play station/computer games	131.7 (306.9)	96.2 (281.8)	103.1 (309.4)	0.061
Computer/internet	74.9 (215.7)	70.5 (229.9)	69.0 (270.1)	0.185
Homework	363.1 (410.6)	415.2 (489.0)	516.6 (717.0)	0.392
Play indoors with toys	136.7 (277.4)	164.1 (315.4)	193.7 (359.0)	0.742
Sitting talking	112.7 (296.5)	170.3 (400.2)	293 (757.4)	0.052
Talk on the phone	16.8 (60.0)	38.2 (175.5)	67.1 (231.9)	**0.001**
Listen to music	177.4 (402.3)	121.9 (258.1)	118.3 (253.2)	0.118
Playing musical instrument	7.6 (37.4)	5.1 (62.3)	2.9 (27.9)	**0.005**
Playing board games/cards	15.7 (88.0)	15.9 (75.9)	27.4 (129.3)	0.249
Reading	98.1 (222.4)	146.6 (294.2)	250.2 (420.4)	**0.001**
Art	40.2 (128.3)	44.7 (169.5)	49.1 (234.6)	0.187
Imaginary play	24.0 (115.5)	72.3 (197.2)	89.1 (279.9)	**0.001**
Travel by car/bus	154.7 (357.6)	105.7 (296.1)	160.3 (372.4)	**0.032**
Total sedentary behavior	1819.4 (1680.0)	2176.5 (2168.9)	2687.0 (2673.5)	0.008

ASD: Autism spectrum disorders; CP: Cerebral palsy; ID: Intellectual disability; SD: Standard deviation.

Table 3 represents the sedentary behaviors of participants. The mean of the total sedentary behavior duration in the ASD group (1819.4 mins/week, SD: 1680) was significantly lower than in the CP group (2687 mins/week, SD: 2673; P = 0.007) but not ID group (2176 mins/week, SD: 2168.9; P = 0.525). There was also no significant difference between children with CP and ID concerning the time spent on sedentary behavior (P = 0.106).

Sociodemographic contributing factors

Tables 4-6 show the details of contributing factors for moderate to vigorous physical activities (MVPA) and sedentary behaviors in the ASD, ID, and CP groups, respectively. OPA was significantly lower in females (mean = 5.6, SD = 11.1) than males (mean = 61.6, SD = 136) in children with ASD (P = 0.045). Also, in the ASD group, non-OPA (P = 0.032) and sedentary behavior (P = 0.02) levels were significantly different in children of mothers with various educational levels (Table 4). Males in the ID group had higher MVPA (P < 0.001), OPA (P < 0.001), and non-OPA (P = 0.001) levels than the females. Household status (P = 0.018) and age (P = 0.004) were associated with OPA, while the presence of musculoskeletal disorders (P = 0.041) and household status (P = 0.008) were associated with sedentary behavior in the ID group (Table 5). Additionally, in this group, childcare status was associated with MVPA (P = 0.021) and non-OPA (P = 0.023). Gender was associated with MVPA (P = 0.091), OPA (P = 0.045), and sedentary behavior (P = 0.002) in children with CP. Also, household status (P = 0.018) and father's education (P = 0.029) were associated with sedentary behavior and OPA, respectively (Table 6).

DISCUSSION

Regular OPA and general PA help enhance psychosocial and health outcomes[29]. On the other hand, sedentary behaviors can indirectly increase the risk of various health conditions. It is worth noting that children and adolescents with disabilities have a lower participation rate in PA, putting them at higher risk for complications[30], which can cause significant challenges for the child, their families, and society[30]. Thus, we aimed to examine the participation rate of OPA, PA, and sedentary behaviors among children with neurodevelopmental disorders in a new sample from a developing country.

Interestingly, our findings showed that the amount of OPA is lower than non-OPA in all ASD, CP, and ID groups. Despite the known positive effects of group-based OPA in overall social functioning in children[23], it seems that the parents/caregivers of children with neurodevelopmental disorders still do not take advantage of regular OPA as a non-medical treatment for their children. Papadopoulos *et al*[31] examined parent-reported barriers to OPA, reported a lack of children's happiness and motivation during OPA as the main existing barriers to OPA among individuals with neurodevelopmental disorders. However, it seems that other hypothetical major barriers, such as the lack of appropriately adapted OPA programs and parents' unawareness of OPA's benefits, are also playing a role in developing

Table 4 Associations between contributing factors, moderate to vigorous physical activities,and sedentary behaviors in autism spectrum disorders group

Domain	Variable		MVPA (mins/week)	*P* value	OPA (mins/week)	*P* value	Non-OPA (mins/week)	*P* value	SB (mins/week)	*P* value
Individual	Gender	Male (*n* = 239)	276.7 (377.9)	0.127	61.6 (136.0)	**0.045**	215.1 (299.3)	0.310	1835.6 (1686.0)	0.418
		Female (*n* = 9)	100.6 (105.8)		5.6 (11.1)		95.0 (105.2)		1388.7 (1536.3)	
	Age	6-11 yr (*n* = 143)	308.1 (423.1)	0.381	64.3 (148.7)	0.484	243.8 (345.4)	0.313	1897.70 (1738.69)	0.733
		12-14 yr (*n* = 72)	200.1 (237.5)		48.5 (81.0)		151.5 (193.4)		1728.3 (1538.7)	
		15-18 yr (*n* = 33)	259.7 (319.3)		62.9 (159.4)		196.8 (218.6)		1679.1 (1747.5)	
	Musculoske-letal disorder	No (*n* = 221)	264.4 (380.2)	0.094	57.7 (136.1)	0.054	206.7 (301.6)	0.140	1774.4 (1666.3)	0.242
		Yes (*n* = 27)	318.9 (307.8)		74.6 (115.9)		244.2 (239.1)		2187.7 (1778.6)	
Familial/social	Household	Owner (*n* = 131)	252.2 (362.2)	0.897	59.1 (142.0)	0.880	193.1 (262.6)	0.985	1803.0 (1625.8)	0.986
		Tenant (*n* = 92)	288.3 (397.6)		65.7 (137.0)		222.7 (324.9)		1832.8 (1801.9)	
		Other (*n* = 15)	234.4 (223.1)		52.0 (74.8)		182.4 (206.6)		1846.0 (1729.3)	
	Child care	Two parents (*n* = 207)	285.5 (389.1)	0.258	63.8 (144.5)	0.624	221.8 (304.0)	0.325	1906.3 (1698.4)	0.493
		Single parent (*n* = 17)	202.9 (296.8)		29.4 (35.6)		173.5 (297.9)		1415.0 (1399.3)	
		Other (*n* = 1)	-		-		-		-	
	Father's education	Lower than diploma (*n* = 39)	309.3 (426.0)	0.335	58.5 (144.6)	0.060	250.8 (367.3)	0.672	1782.3 (1637.1)	0.099
		Diploma (*n* = 70)	264.2 (439.7)		62.4 (189.2)		201.8 (295.2)		1526.7 (1584.9)	
		Higher than diploma (*n* = 128)	269.0 (324.6)		60.7 (93.9)		208.3 (277.0)		2012.8 (1637.1)	
	Mother's education	Lower than diploma (*n* = 37)	229.9 (352.3)	0.076	37.8 (75.8)	0.443	192.0 (342.8)	**0.032**	1218.8 (1694.3)	**0.020**
		Diploma (*n* = 85)	323.1 (433.6)		70.0 (177.3)		253.1 (306.6)		1696.5 (1708.2)	
		Higher than diploma (*n* = 120)	251.5 (337.2)		59.9 (113.4)		191.6 (275.1)		1898.4 (1607.9)	
	Father's age	< 35 yr (*n* = 13)	204.2 (222.6)	0.484	36.9 (46.1)	0.496	167.3 (217.1)	0.538	1656.0 (2499.9)	0.223
		35-49 yr (*n* = 182)	297.0 (403.1)		64.7 (144.8)		232.3 (320.8)		1912.5 (1690.2)	
		≥ 50 yr (*n* = 40)	202.6 (244.1)		44.5 (93.9)		158.1 (190.8)		1472.0 (1329.6)	
	Mother's age	< 35 yr (*n* = 81)	327 (456.6)	0.168	71.7 (181.7)	0.544	255.4 (334.3)	0.228	1822.7 (1935.8)	0.218
		35-49 yr (*n* = 149)	258.2 (334.1)		56.3 (107.4)		202.0 (283.3)		1866.2 (1545.9)	
		≥ 50 yr (*n* = 13)	132.7 (177.1)		27.3 (53.4)		105.4 (132.2)		1123.5 (1129.0)	

OPA: Organized physical activity; SB: Sedentary behaviors MVPA: Moderate to vigorous physical activities

Table 5 Associations between contributing factors, moderate to vigorous physical activities,and sedentary behaviors in intellectual disability group

Domain	Variable		MVPA (mins/week)	*P* value	OPA (mins/week)	*P* value	Non-OPA (mins/week)	*P* value	SB (mins/week)	*P* value
Individual	Gender	Male (*n* = 219)	208.2 (295.8)	< **0.001**	63.7 (114.2)	< **0.001**	144.5 (224)	**0.001**	2183 (1916.7)	0.248
		Female (*n* = 247)	140.7 (252.1)		38.5 (86.9)		102.2 (195.2)		2170.7 (2374.1)	
	Age	6-11 yr (*n* = 176)	179.1 (276.2)	0.355	43.6 (104)	**0.004**	135.5 (212.8)	0.248	2200.6 (2193.2)	0.831
		12-14 yr (*n* = 147)	164.0 (299.1)		47.0 (101.6)		117.0 (237.6)		2090.5 (2149.9)	
		15-18 yr (*n* = 143)	172.9 (249.1)		62.2 (97.2)		110.7 (174.0)		2235.0 (2170.9)	
	Musculoskeletal disorder	No (*n* = 396)	171.2 (263.1)	0.676	49.4 (101.4)	0.775	121.8 (200.8)	0.421	2249.2 (2170.2)	**0.041**
		Yes (*n* = 70)	179.6 (338.2)		56.0 (101.2)		123.6 (258.1)		1764.9 (2130.5)	
Familial/social	Household	Owner (*n* = 239)	179.7 (250.7)	0.054	57.4 (106.3)	**0.018**	122.2 (185.4)	0.075	2413.6 (1994.4)	**0.008**
		Tenant (*n* = 178)	161.5 (295.1)		42.0 (96.9)		119.5 (225.7)		1994.7 (2415.6)	
		Other (*n* = 24)	138.6 (170.1)		39.2 (59.5)		99.4 (159.7)		2346.2 (2007.6)	
	Child care	Two parents (*n* = 350)	183.7 (286.0)	**0.021**	52.9 (108.3)	0.282	130.8 (216.6)	**0.023**	2205.3 (2121.6)	0.144
		Single parent (*n* = 48)	130.2 (216.1)		41.8 (74.0)		88.4 (172.9)		2093.1 (2189.2)	
		Other (*n* = 10)	53.6 (125.9)		20.0 (43.2)		33.6 (96.2)		1282.0 (2451.6)	
	Father's education	Lower than diploma (*n* = 217)	177.7 (298.1)	0.446	51.5 (104.6)	0.633	126.2 (231.8)	0.233	2098.5 (2151.7)	0.421
		Diploma (*n* = 134)	171.4 (237.4)		39.2 (64.7)		132.23 (194.40)		2442.4 (2266.8)	
		Higher than diploma (*n* = 96)	175.9 (286.8)		68.0 (136.5)		107.9 (185.7)		2215.7 (2104.4)	
	Mother's education	Lower than diploma (*n* = 215)	185.7 (307.1)	0.575	52.9 (112.4)	0.575	132.8 (235.9)	0.552	2175.8 (2399.6)	0.6
		Diploma (*n* = 159)	157.0 (215.0)		41.4 (74.7)		115.6 (173.2)		2215.3 (1901.2)	
		Higher than diploma (*n* = 70)	178.9 (315.7)		64.0 (124.5)		114.8 (217.4)		2256.5 (2108.8)	
	Father's age	< 35 yr (*n* = 22)	140.2 (173.3)	0.367	36.0 (53.8)	0.927	104.1 (151.5)	0.059	1894.1 (1841.9)	0.756
		35-49 yr (*n* = 289)	176.2 (256.7)		49.5 (100.2)		126.7 (198.5)		2239.32 (2106.00)	
		≥ 50 yr (*n* = 135)	179.1 (333.0)		57.1 (115.1)		122.0 (245.7)		2237.8 (2381.8)	
	Mother's age	< 35 yr (*n* = 90)	169.5 (248.4)	0.953	42.0 (80.7)	0.542	127.5 (202.5)	0.759	1863.4 (1888.8)	0.326
		35-49 yr (*n* = 297)	165.6 (252.1)		49.5 (100.0)		116.1 (191.6)		2272.5 (2211.1)	
		≥ 50 yr (*n* = 62)	218.9 (406.3)		69.4 (139.0)		149.5 (297.4)		2278.8 (2403)	

OPA: Organized physical activity; SB: Sedentary behaviors MVPA: Moderate to vigorous physical activities

Table 6 Associations between contributing factors, moderate to vigorous physical activities,and sedentary behaviors in cerebral palsy group

Domain	Variable		MVPA (mins/week)	*P* value	OPA (mins/week)	*P* value	Non-OPA (mins/week)	*P* value	SB (mins/week)	*P* value
Individual	Gender	Male (*n* = 146)	80.9 (163.5)	**0.019**	19.1 (53.5)	**0.045**	61.9 (125.1)	0.107	2236.2 (2531.7)	**0.002**
		Female (*n* = 160)	128.7 (294.4)		33.4 (105.7)		95.3 (260.3)		3098.2 (2740.2)	
	Age	6-11 yr (*n* = 143)	126.4 (288.0)	0.665	23.9 (70.6)	0.681	102.6 (267.5)	0.471	2250.8 (2326.4)	0.076
		12-14 yr (*n* = 82)	98.8 (229.7)		40.5 (130.7)		58.3 (137.6)		3061.3 (2850.2)	
		15-18 yr (*n* = 81)	76.9 (143.5)		17.2 (33.9)		59.7 (127.1)		3078.0 (2963.1)	
	Musculoske-letal disorder	No (*n* = 228)	113.9 (269.2)	0.907	26.8 (83.9)	0.633	87.0 (233.1)	0.976	1771.6 (2807.1)	0.623
		Yes (*n* = 78)	82.7 (131.1)		25.8 (89.1)		56.9 (98.4)		2439.5 (2235.6)	
Familial/social	Household	Owner (*n* = 108)	98.5 (203.5)	0.586	28.0 (85.8)	0.543	70.5 (173.3)	0.418	2411.4 (2769.4)	**0.018**
		Tenant (*n* = 141)	106.8 (248.9)		18.4 (53.4)		88.4 (241.6)		3060.0 (2509.6)	
		Other (*n* = 36)	108.1 (308)		47.1 (150.1)		61.1 (179.3)		221.3 (2841.7)	
	Child care	Two parents (*n* = 242)	115.3 (260.2)	0.828	28.7 (91.0)	0.901	88.6 (227.2)	0.972	2686.2 (2707.5)	0.429
		Single parent (*n* = 25)	60.0 (85.1)		11.6 (21.0)		48.4 (72.0)		3329.4 (2927.9)	
		Other (*n* = 4)	36.3 (66.0)		11.3 (22.5)		25.0 (43.6)		3147.5 (2116.5)	
	Father's education	Lower than diploma (*n* = 122)	114.3 (231.1)	0.182	36.5 (110.3)	**0.029**	77.8 (168.6)	0.257	2879.7 (2684.7)	0.261
		Diploma (*n* = 89)	127.0 (324.4)		21.1 (68.0)		105.9 (311.7)		2847.8 (3060.3)	
		Higher than diploma (*n* = 67)	60.6 (108.2)		14.8 (41.7)		45.8 (89.6)		2199.7 (2229.7)	
	Mother's education	Lower than diploma (*n* = 105)	103.0 (183.5)	0.604	34.7 (99.0)	0.059	68.2 (137.7)	0.908	2514.6 (2757.7)	0.423
		Diploma (*n* = 132)	116.2 (309.6)		22.0 (82.3)		94.2 (279.2)		2967.4 (2822.2)	
		Higher than diploma (*n* = 54)	65.5 (104.8)		17.0 (44.8)		48.5 (86.8)		2642.4 (2291.8)	
	Father's age	< 35 yr (*n* = 24)	99.8 (133.8)	0.117	45.0 (114.2)	0.33	54.8 (73.4)	0.245	2598.5 (2184.7)	0.966
		35-49 yr (*n* = 206)	106.7 (271.1)		22.7 (73.8)		84.0 (240.2)		2711.8 (2839.5)	
		≥ 50 yr (*n* = 51)	103.4 (150.2)		30.7 (108.7)		72.7 (110.4)		2593.2 (2488.7)	
	Mother's age	< 35 yr (*n* = 99)	102.8 (205.7)	0.740	27.4 (84.1)	0.978	75.3 (188.3)	0.802	2829.4 (2773.4)	0.595
		35-49 yr (*n* = 179)	108.2 (264.9)		25 (85.9)		83.1 (226.5)		2639.1 (2696.7)	
		≥ 50 yr (*n* = 16)	40.9 (56.1)		18.4 (35.3)		22.5 (32.0)		3098.4 (2400.9)	

OPA: Organized physical activity; SB: Sedentary behaviors MVPA: Moderate to vigorous physical activities

societies.

In addition, our study showed that among our participants, children with ASD had the highest level of OPA, non-OPA, and total PA, followed by children with ID and then CP. Besides, our study showed that although the pattern and specific type of sedentary behaviors were different among the three groups, children with ASD were similar to ID and better than the CP group. Moreover, regarding the intensity of PA, children with ASD demonstrated the highest levels of moderate and vigorous PA compared to CP and ID groups. Although previous investigations reported a lesser amount of MVPA in children with ASD compared to their TD peers[29,32], our study showed that among two other neurodevelopmental disorders, such as CP and ID, children with ASD would report better results. According to the world health organization (WHO), it is recommended 60 min per day (300 min per week) of MVPA to gain health benefits of PA for children[33]; thus, our study showed that all three groups of participants, on average, participated in less MVPA than what is recommended for children. However, due to the lack of a developed standard of PA or OPA participation for children and adolescents with neurodevelopmental disorders, such interpretation should be made with caution.

To our knowledge, this is one of the first reports representing the amount of OPA/non-OPA as well as sedentary behaviors in children and adolescents with ASD in comparison to other neurodevelopmental disorders such as ID and CP. This finding highlights the importance of considering the health conditions (*e.g.*, motor *vs* non-motor limitation) of children with neurodevelopmental disorders in OPA participating. For example, children with CP might have more motor limitations than children with ASD and ID. Designing adapted OPA specific for each neurodevelopment disorder is of paramount importance for increasing the rate of OPA participation in these populations. As an important limitation, previous studies only examined the general PA participation in ASD and similar disorders. For example, examining ASD with TD peers, data showed an association between lower levels of PA participation and an increase in medical complications such as obesity and chronic illness[11,34]. Recent studies have shown that the issue has worsened because of the COVID-19 pandemic, quarantine, and social distancing[35,36].

Although, according to evidence, the level of PA in children and adolescents with ASD is lower than TD ones, our study showed that, at least in part, the PA status of children and adolescents with ASD is better than other children with neurodevelopmental disorders such as children with CP and ID. It highlights the urgent need to design and develop strategies to enhance the PA and OPA levels for all children and adolescents with neurodevelopmental disorders, which might be challenging due to the lack of studies and the inefficacy of current interventions[37]. This issue warrants much more attention in developing countries which need both increase the general awareness of people and design novel strategies for enhancing adapted PA behavior in individuals with neurodevelopmental disorders. According to theories and frameworks[31], the opportunities for adapted PA/OPA must be intrinsically rewarding to encourage acquiring life skills and reassure peer relationships, parental involvement, and the sense of belonging to a bigger community[38].

Children with CP had the least PA time compared to ASD and ID, possibly related to the higher number of physical and movement incapacities. On the other side, we recruited children and adolescents with ASD from special schools; usually, children who attend these schools are high functioning and consequently do not have the limitations of children with low-functioning ASDs (comorbid with ID and other disabilities). Consequently, they may also have the potential to do more deliberate and regular activities, improving their PA level than more physically and mentally disabling disorders such as CP and ID. Given the above, it seems necessary to develop standards for PA/OPA participation rate in children and adolescents with neurodevelopmental disorders generally and specifically for each group based on the amount of physical and cognitive limitations.

In addition, regarding the contributing factors, our results suggest that gender, parent's education, and childcare status might be related to PA and sedentary behaviors. Factors contributing to enhancing the amount of PA may have an adverse effect on sedentary behaviors and vice versa[39,40]. In the general population, individuals with older age, female gender, comorbidities, the need for movement equipment, or higher BMI are more prone to engage in less PA and more sedentary behaviors[39]. In previous investigations, factors such as symptom severity, gender, having other comorbidities, using mobility equipment, and household status have been reported to contribute to PA participation rate in children with ID and CP[13,14].

The current study is unique in its sample and measures; however, it is not without limitations. The recall bias and the selection of the participants from special schools were from study limitations. In addition, we had to use cross-sectional data for physical activity behavior, and we could not scrutinize the potential effects of data changes over time. Nevertheless, the relatively sizable number of participants could be accounted as one of the important strengths of the current study. This might authenticate and increase the validity of the result in the study despite its limitation.

CONCLUSION

The current study showed that PA behavior in ASD, ID, or CP groups was lower than expected, highlighting the need to support PA/OPA opportunities by designing targeted and adapted programs to decrease unhealthy sedentary behaviors in these groups.

ARTICLE HIGHLIGHTS

Research background

There is little data on physical activity (PA), organized PA (OPA), and sedentary behaviors in children with neurodevel-

opmental disorders in developing countries.

Research motivation

In this large-scale study, we evaluated PA levels among children with neurodevelopmental disorders in the context of a developing country to help identify the groups which benefit the most from the interventions to improve PA levels, which can be a basis for future studies.

Research objectives

To examine OPA, non-OPA, and sedentary behaviors and their associated factors in children and adolescents with autism spectrum disorders (ASD), cerebral palsy (CP), and intellectual disability (ID).

Research methods

A total of 1020 children and adolescents with ASD, CP, and ID living in Tehran between 2011 and 2021 were assessed regarding the child and family information as well as the Children's Leisure Activities Study Survey.

Research results

The results showed that the OPA level was significantly lower than non-OPA in all groups. Moderate to vigorous PA levels were higher among children with ASD compared to children with CP and ID.

Research conclusions

The PA levels are lower than the recommended levels in children with neurodevelopmental disabilities living in a developing country, and there is a need for interventions to improve PA levels, especially OPA, in this group.

Research perspectives

Future studies should focus on evaluating PA levels in children with neurodevelopmental disabilities in other developing countries, and aim to design intervention to improve OPA and total PA in this group.

FOOTNOTES

Author contributions: Memari A was the guarantor; Nakhostin-Ansari A, Shayestehfar M, and Memari A designed and implemented the study; Nakhostin-Ansari A analyzed the data; Nakhostin-Ansari A, Shayestehfar M, Gorgani F, and Hasanzadeh A wrote the initial draft of the manuscript; and all authors read and approved the final version of the manuscript.

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ORIGINAL ARTICLE

Observational Study

Influence of resilience on depression among nurses in clean operating departments: The mediating effect of life satisfaction

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Abstract

BACKGROUND

A clean operating room is an important part of surgical and critical treatment in hospitals. The workload is substantial, the pace is rapid, and the working environment is intense; therefore, nurses who work in clean operating rooms are constantly challenged, which can lead to anxiety, depression, and other mental health issues. Life satisfaction and resilience are important factors that ensure mental health. Therefore, exploring the mediating role of life satisfaction in the influence of resilience on depression among nurses in clean operating rooms can help improve nursing services and teamwork.

AIM

To explore the mediating effect of satisfaction on the influence of resilience on depression among nurses in a clean operating department.

METHODS

From April to November 2022, 196 nurses from the Department of Clean Operating at Harbin Medical University Cancer Hospital participated in this study. Participants were selected using convenience sampling. Participants' gender, age, marital status, position, length of service, personal monthly income, daily working hours, employment status, and professional title were collected, and the Connor-Davidson resilience scale, satisfaction with life scale, and self-rating depression scale were used to evaluate resilience, life satisfaction, and depression. The researchers conducted professional training in advance, introduced the research methods to the participants before the investigation, and explained the study's significance and purpose. Surveys were distributed and collected on-site. Each questionnaire took 30 min to complete.

RESULTS

The average scores for life satisfaction, resilience, and depression were 3.13 (±

0.28), 4.09 (± 0.78), and 56.21 (± 8.70), respectively. The correlation between resilience and depression was negative (r = -0.829, P < 0.01). Life satisfaction was positively related to resilience (r = 0.855, P < 0.01) and negatively related to depression (r = -0.778, P < 0.01). The relationship between resilience and depression was partially mediated by life satisfaction. The value of the mediating effect was -6.853 (26.68% of the total effect).

CONCLUSION

Life satisfaction partially mediates the link between resilience and depression among nurses in clean operating departments.

Key Words: Psychological resilience; Depression; Life satisfaction; Clean operation department; Nurses; Mediating effect

Core Tip: The professional and psychological qualities of clean operating department nurses affect their operation success. Clinical practice emphasizes the importance of the mental health of nurses in operating rooms. This study found that, for nurses working in clean operating departments, resilience was positively correlated with life satisfaction and negatively correlated with depression, indicating that resilience can increase life satisfaction and decrease depression. Life satisfaction mediated the relationship between resilience and depression. This suggests that nurses in clean operating departments should improve their life satisfaction and resilience to adversity to improve their mental health.

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INTRODUCTION

The psychological health of nursing staff has received increasing attention in recent years[1,2]. Relevant studies have shown that heavy, harsh, and demanding working conditions; medical requirements of patients and their families; public opinion; difficulty balancing work and family; salary; and other factors affect the psychological well-being of nursing personnel[3,4]. A clean operating department is necessary for hospitals to provide surgical procedures and treat critically ill patients, and the workload is closely related to the number and difficulty of operations[5,6]. Especially in tertiary hospitals, all types of difficult and complicated diseases are more complex, and new surgical techniques are rapidly being developed. In addition, in clean operating departments, the workload is large, rhythm is fast, and intensity is high□ constantly challenges nurses in clean operating departments, and can easily result in negative emotional states, such as depression and anxiety, and ultimately, psychological problems.

Life satisfaction is the overall cognitive appraisal of a person's level of satisfaction in their life[7]. Life satisfaction is a crucial factor in achieving good mental health and directly associated with various psychological, behavioral, interpersonal, and social factors such as reduced stress, externalized behavior, and internalized problems[8,9]. Therefore, life satisfaction is one of the most important indicators used to gauge an individual's level of happiness and overall quality of life. Further, resilience plays a significant role in positive psychology[10]. Resilience is a psychological quality that allows individuals to cope well with adversity and a protective factor for individual mental health[11,12]. Previous research has reported that life satisfaction is positively associated with individual psychological health and negatively correlated with depression[13,14]. The results of studies conducted with different groups have shown that individual life satisfaction is positively correlated with resilience[15-17].

However, few studies have examined the correlations among resilience, depression, and life satisfaction in nurses in clean operating departments. This study aims to explore the mediating role of life satisfaction in the effects of resilience on depression and to provide a scientific basis for improving resilience, increasing life satisfaction, and reducing the occurrence of depression among nursing staff in clean operating departments.

MATERIALS AND METHODS

Participants

From April to November 2022, 196 nurses from the Department of Clean Operating at Harbin Medical University Cancer Hospital took part in this study. Participants were selected using convenience sampling. The inclusion criteria were as follows: (1) Currently employed on the nursing staff with at least one year of job experience; (2) no personal or family history of mental illness; and (3) no psychotropic drugs use in the last year. The exclusion criteria were as follows: (1) Non-frontline nurses; (2) nurses who took long-term personal, sick, or maternity leave during the study period; (3) nurses

from other departments; (4) nurses participating in other clinical studies; and (5) nurses who were working on an internship or in training.

Basic information survey

The general demographic variables questionnaire designed by this research team was used to collect basic information on the participants, including gender, age, marital status, position, length of service, personal monthly income, daily working hours, employment, and professional title.

Life satisfaction survey

The satisfaction with life scale (SWLS) by Diener *et al*[18] was used to measure life satisfaction. The SWLS includes five items, each rated on a Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). In this study, average scores across the five life satisfaction questions ranged from 1 to 7 points. The SWLS has been shown to be trustworthy and is often utilized in quality-of-life research conducted in Chinese populations[19].

Resilience survey

Resilience was evaluated using the Chinese version of the Connor-Davidson resilience scale (CD-RISC)[20], which has 25 items. Responses were rated on a five-point Likert scale ranging from 0 (never) to 4 (always). The overall scale's average value ranged from 0 to 4, and higher scores indicated greater resilience.

Depression survey

The Self-Rating Depression Scale (SDS), compiled by Zung[21], was used to assess depressive symptoms among the participants in the current or previous week. The scale has 20 questions, 10 positive and negative, rated on a four-point Likert scale (no, sometimes, often, and continuously, rated between 1-4 points respectively). The original score was multiplied by 1.25 to take the integer as the standardized score, and a standardized score > 53 was considered to indicate the presence of depressive symptoms.

Quality control

Prior to beginning the study, the researchers conducted a professional training session in which they introduced the research methods to the participants with unified guidance language and explained the study's significance and purpose. Questionnaires were distributed in person and collected immediately after participants completed them. Participants took approximately 30 min to complete the survey. After eliminating invalid questionnaires, the effective questionnaire recovery rate was 90.8% (178 out of 196). Questionnaire review and score entry was completed by two researchers.

Statistical analysis

Data collected in this study were analyzed using IBM SPSS version 26.0. The significance threshold for each two-sided statistical test was set at $P < 0.05$. The mean, standard deviation (SD), number (n), and percentage (%) were used for descriptive statistics of participant demographics and other factors. A t-test and single-factor analysis of variance were used to compare the variations among classification crowds. Pearson correlation analysis was used to examine the relationship between continuous variables. The mediating effects were examined using Hayes' Process Macro Model 4. To determine whether the regression coefficient of the mediating effect of the estimated chain of 5000 samples in the initial data was significant by employing repeated random sampling, it was determined using a bootstrap 95% confidence interval (CI). If the 95%CI did not contain zero, the indirect effect was considered statistically significant.

RESULTS

Participant characteristics

A total of 196 surveys were distributed, and 178 valid surveys were returned, for a response rate of 90.8%. The participants' ages ranged between 22-52 years, with a mean age of 33.69 years (SD = 6.99). Employment duration ranged between 1-30 years, with a mean of 10.80 years (SD = 7.12). Descriptive statistics are shown in Table 1.

Correlations among resilience, life satisfaction, and depression

Resilience was negatively correlated with depression ($r = -0.829$, $P < 0.01$) and positively correlated with life satisfaction ($r = 0.855$, $P < 0.01$). Life satisfaction was negatively correlated with depression ($r = -0.778$, $P < 0.01$) (Table 2).

Analysis of influencing factors of mental resilience, life satisfaction and depression

As shown in Table 3, the results of multi-factor analysis show that gender, age, working time and employment status are the main factors affecting the level of mental resilience; gender, age and working time are the main factors affecting life satisfaction; gender, age, working time and employment status are the main factors affecting depression score.

Mediating effects of life satisfaction between resilience and depression

In testing the mediating effects, resilience was the independent variable, life satisfaction the mediating variable, and depression the dependent variable. Figure 1 depicts the mediation model established in this study. The regression results

Table 1 Sociodemographic characteristics and their differences among primary variables

Variables		*n*	%	Life satisfaction	Resilience	Depression
				mean ± SD	mean ± SD	mean ± SD
Gender	Male	58	32.58	4.23 ± 0.74	3.25 ± 0.23	53.55 ± 7.10
	Female	120	67.42	4.03 ± 0.79	3.06 ± 0.25	57.50 ± 9.13
	t			2.733	31.112	9.262
	P			0.100	< 0.001	0.003
Age	< 30	60	33.71	4.72 ± 0.82	3.27 ± 0.27	51.47 ± 6.95
	30-45	107	60.10	3.79 ± 0.53	3.06 ± 0.26	58.02 ± 8.31
	46-60	11	6.18	3.60 ± 0.33	2.93 ± 0.22	64.55 ± 8.78
	F			44.439	14.769	19.699
	P			< 0.001	< 0.001	< 0.001
Marital status	Married	104	58.43	3.93 ± 0.65	3.10 ± 0.27	56.86 ± 8.46
	Unmarried	48	26.97	4.55 ± 0.90	3.21 ± 0.29	52.79 ± 7.61
	Divorced or other	26	14.61	3.88 ± 0.67	3.09 ± 0.29	59.96 ± 9.69
	F			13.505	2.829	6.824
	P			< 0.001	0.062	0.001
Educational level	Junior college or below	77	43.26	4.07 ± 0.77	3.11 ± 0.30	56.18 ± 8.99
	University degree or above	101	56.74	4.11 ± 0.78	3.14 ± 0.27	56.24 ± 8.52
	t			0.094	0.566	0.002
	P			0.759	0.453	0.966
Professional title	Primary	54	30.34	4.53 ± 0.88	3.21 ± 0.29	53.11 ± 7.89
	Intermediate	110	61.80	3.92 ± 0.64	3.10 ± 0.26	57.61 ± 8.40
	Senior	14	7.87	3.80 ± 0.68	3.04 ± 0.32	57.21 ± 11.32
	F			14.515	3.738	5.169
	P			< 0.001	0.026	0.007
Years of work experience	< 10	79	44.38	4.51 ± 0.83	3.22 ± 0.27	53.06 ± 7.25
	10-19	74	41.57	3.80 ± 0.55	3.07 ± 0.27	58.07 ± 8.52
	20-38	25	14.04	3.63 ± 0.45	2.98 ± 0.25	60.68 ± 10.15
	F			27.726	9.837	11.328
	P			< 0.001	< 0.001	< 0.001
Monthly income (RMB)	< 3000	39	21.91	4.69 ± 0.88	3.25 ± 0.28	51.46 ± 6.89
	3000-5000	118	66.29	3.94 ± 0.66	3.10 ± 0.27	57.55 ± 8.57
	5001-10000	21	11.80	3.83 ± 0.62	3.05 ± 0.28	57.52 ± 9.73
	F			17.594	5.195	8.034
	P			< 0.001	< 0.001	< 0.001
Daily working hours (h)	< 8	49	27.53	3.83 ± 0.54	3.08 ± 0.26	57.86 ± 9.44
	8-10	129	72.47	4.19 ± 0.83	3.14 ± 0.29	55.59 ± 8.36
	t			7.919	1.694	2.430
	P			0.005	0.195	0.121
Employment status	Formal employee	121	67.98	3.85 ± 0.60	3.08 ± 0.26	58.07 ± 8.72
	Contract employee	57	32.02	4.61 ± 0.85	3.23 ± 0.29	52.26 ± 7.30
	t			46.088	12.488	19.031

P	< 0.001	0.001	< 0.001
Mean	4.09 ± 0.78	3.13 ± 0.28	56.21 ± 8.70

Table 2 Correlations for study variables

Variables	Resilience	Life satisfaction	Depression
Resilience	1		
Life satisfaction	0.855[a]	1	
Depression	-0.829[a]	-0.778[a]	1

[a]*P* < 0.01 (two-tailed), the correlation was significant.

Table 3 Analysis of influencing factors of mental resilience, life satisfaction and depression

Factor	Variables	B	SE	Beta	*t*	*P*
Resilience	Gender	-5.847	0.958	-0.392	-6.101	< 0.001
	Age	-0.861	0.131	-0.857	-6.551	< 0.001
	Daily working hours (h)	-6.947	1.617	-0.443	-4.296	< 0.001
	Employment status	2.297	1.160	0.189	1.979	0.049
Life satisfaction	Age	-0.092	0.011	-0.831	-8.132	< 0.001
	Daily working hours (h)	-0.748	0.176	-0.432	-4.246	< 0.001
	Gender	-0.337	0.104	-0.204	-3.234	0.001
Depression	Age	1.167	0.165	0.937	7.061	< 0.001
	Daily working hours (h)	9.209	2.033	0.474	4.530	< 0.001
	Gender	5.485	1.205	0.296	4.553	< 0.001
	Employment status	-3.422	1.459	-0.227	-2.346	0.02

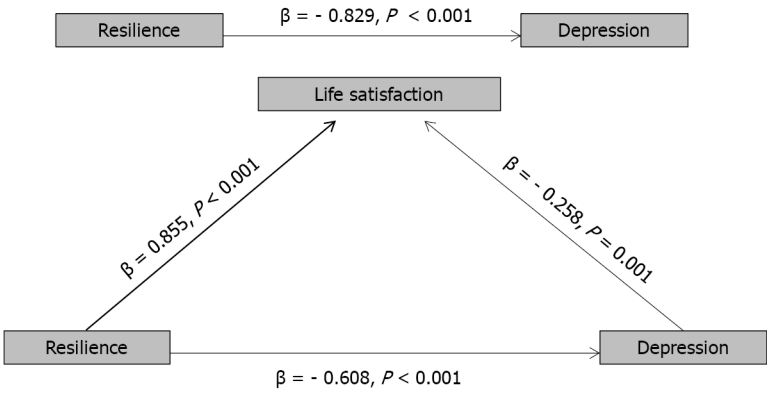

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Figure 1 The model of the mediating role of life satisfaction in the relationship between resilience and depression.

are presented in Table 4. Resilience had a negative and considerable direct predictive effect on depression (β = -0.608, *P* < 0.001). Further, resilience was found to significantly and positively predict life satisfaction (β = 0.855, *P* < 0.001) and negatively predict depression (β = -0.829, *P* < 0.001). Finally, life satisfaction was found to significantly negatively predict depression (β = -0.258, *P* = 0.001).

As shown in Table 5, the 95%CI of the direct effect of resilience-depression was (-23.636, -14.104), excluding 0, indicating that the direct effect was significant (the value of the effect was -18.832, accounting for 73.32% of the total effect). The 95%CI of the indirect effect of resilience-life satisfaction-depression was (-10.546, -3.120), excluding 0, indicating that life satisfaction mediated the relationship between resiliency and depression (the value of the effect was -

Table 4 Regression analysis of the mediating effect of life satisfaction on resilience and depression

Outcome variable	Predictor variable	*R*	R^2	*F*	β	*t*	*P*
Depression	Resilience	0.829	0.687	385.463	-0.829	-19.633	< 0.001
Life satisfaction	Resilience	0.855	0.732	480.175	0.855	21.913	< 0.001
Depression	Resilience	0.839	0.704	208.553	-0.608	-7.656	< 0.001
	Life satisfaction				-0.258	-3.257	0.001

Table 5 Mediating effect of life satisfaction on resilience and depression

Model pathways	Effect	Boot SE	95%CI		Relative mediation effect, %
			Lower	Upper	
Resilience-life satisfaction-depression	-6.853	1.920	-10.546	-3.120	26.68%
Resilience-depression	-18.832	2.444	-23.636	-14.104	73.32%
Total mediation effect	-25.685	2.515	-23.794	-14.007	-

95%CI: 95% confidence interval.

6.853, accounting for 26.68% of the total effect).

DISCUSSION

The professional and psychological qualities of nurses working in clean operating departments are important factors that affect the success of an operation[22,23]. Maintaining the mental health of nurses in operating departments has become a focus of clinical practice. that the nurses who participated in this study had a mean depression score of 56.21 (± 8.70) points, which exceeded the critical value for the norm score on the Chinese SDS, which is consistent with previous research[24,25]. Clean operating room nurses not only face fast work rhythms and heavy workloads but also need to constantly improve their professional skills[26,27]. In addition, the operating room is an important place to rescue critically ill patients, and surgical nurses often need to complete emergency rescue tasks, which can impact on their mental health.

This study found that, compared with female nurses in clean operating departments, male nurses had higher resilience and life satisfaction scores and lower depression scores, which may be related to gender differences in personality traits. The results also showed that older respondents had lower resilience and life satisfaction scores, and higher depression scores, compared with younger respondents. This may be due to older nurses often being required to deal with more complex work because of their rich work experience, resulting in increased work pressure and, subsequently, more psychological difficulties. Regarding marital status, the findings showed that, compared with unmarried nurses, nurses whose marital status was married, divorced, or other had lower resilience scores and higher depression scores. This may be because married nurses tend to receive family support and help, and can often obtain psychological comfort in their marriage. This study further found that, compared with nurses with intermediate and senior professional titles, those with junior professional title had lower resilience and life satisfaction scores and higher depression scores. This may be related to the fact that pressure to receive a promotion often negatively affects the mental health of those with low-level professional titles. In this study, compared to nurses with less than ten years of work experience, those in the groups with 10-19 or 20-38 years of work experience had lower resilience and life satisfaction scores and higher depression scores. This may be because nurses with extensive work experience have experienced more problems that can arise in emergency surgery, high-risk patients, medical problems, and job promotions, resulting in greater psychological pressure. Compared with those with a personal monthly income < 3000 yuan, nurses with a personal monthly income of 3000-5000 yuan or 5001-10000 yuan had lower resilience and life satisfaction scores and higher depression scores, which may be related to higher income indicating more job requirements, promotion pressure, and family expectations. In addition, compared with contract nurses, formal nurses had lower resilience and life satisfaction scores and higher depression scores. This may be because formal nurses must deal with administrative work while also completing nursing work and face a more stringent assessment mechanism.

This study found that resilience among the participants was positively correlated with life satisfaction scores and negatively associated depression scores. This indicates that, among nurses working in clean operating departments, the better the resilience, the greater the life satisfaction and lower the depression, which is in accordance with the findings of previous studies[28,29]. Good resilience and life satisfaction are indicators of less psychological difficulty. As a protective factor for adversity, resilience can mobilize individuals to use their own strengths and resources, mitigate the negative impact of risk factors, and ultimately reduce the probability of negative consequences while increasing that of positive

outcomes. These positive outcomes will increase life satisfaction, so that the individual's cognition of people and things related to it is more positive. In addition, nurses will have more positive experiences in life, work, and study, resulting in a decreased risk for psychological problems[30,31].

This study's findings indicate that the connection between resilience and depression is partially mediated by life satisfaction among nurses working in a clean operating department. The value of the effect was -6.853, accounting for 26.68% of the total effect. Related studies have shown that the higher an individual's resilience, the higher their life satisfaction, and high life satisfaction indicates good mental health and low depressive symptoms[32,33]. One characteristic of highly resilient individuals is that they can maintain a high level of life satisfaction in a complex environment, and the positive emotional experience generated by high life satisfaction reduces depression[34,35]. In view of the psychological status of nurses in the operating room, hospitals should regularly carry out psychological and physiological assessment activities for nurses in the operating room, understand the source of stimuli and the causes of nurses' depression, and carry out targeted intervention measures to help nurses decompress psychologically, relieve fatigue and boredom, and improve their life satisfaction and psychological resilience. At the same time, the hospital should further deepen the reform of management mode, establish the professional ethics of medical staff, stimulate the enthusiasm and standardization of nurses' work, and create a good working atmosphere. In addition, we suggest that the hospital actively take targeted intervention measures to optimize the working state of nurses by improving their psychological quality and mental resilience, and finally improve their life satisfaction. For example, experts are invited to hold lectures regularly, and nurses are trained to endure hardships and overcome setbacks through practical experience or typical cases. Psychological lectures, cognitive behavior intervention, relaxation training and other activities were carried out for nurses to help them improve their physical and mental state, psychological resilience and life satisfaction.

However, several factors can affect the mental health of nurses in clean operating departments, such as work boredom, work pressure, job burnout, and lack of social support. This study selected only one direction for in-depth discussion, which is a limitation. In future studies, we hope to further analyze other factors. To improve the mental health of nurses in clean operating departments to provide a more reliable theoretical basis.

CONCLUSION

Depression scores were negatively correlated with resilience. Life satisfaction was positively related to resilience and negatively related to depression. The connection between resilience and depression was partially mediated by life satisfaction among nurses working in a clean operating department.

ARTICLE HIGHLIGHTS

Research background

A clean operating department is important for hospitals to implement surgical treatments and attend to critically ill patients. These departments have a large workload, fast rhythm, and high intensity. The working environment in clean operating departments constantly challenges nurses and can easily lead to negative mental states, such as despair and anxiety, and ultimately, psychological problems. However, ensuring the mental health of nurses in clean operating departments is key to the normal functioning of hospital operating rooms.

Research motivation

A crucial determinant of a person's subjective well-being and quality of life is their level of life satisfaction. Resilience is a protective factor for individual mental health. Both are important factors in ensuring mental health. Therefore, exploring the mediating role of life satisfaction in the effects of resilience on depression among nurses in clean operating departments can provide a reference for promoting harmonious development among nursing teams in operating rooms and improving the quality of nursing services.

Research objectives

To investigate how depression and resilience are related and the possible mediating role of life satisfaction in this association among nurses in clean operating departments and provide a scientific basis for increasing their resilience and life satisfaction, and reducing the occurrence of depression.

Research methods

A total of 196 nurses from three clean operating departments in one hospital were selected using convenience sampling. The Connor-Davidson resilience scale, satisfaction with life scale, and self-rating depression scale (SDS) were used to evaluate resilience, life satisfaction, and depression.

Research results

The mean depression score for nurses in the clean operating department was 56.21 (± 8.70), which exceeded the critical value of the norm score for the Chinese SDS. Nurses' resilience was positively correlated with life satisfaction and negatively correlated with depression. Life satisfaction served as a partial mediator between resilience and depression in

the nurses in the clean operating department, with a mediation effect value of -6.853, accounting for 26.68% of the total effect.

Research conclusions

Life satisfaction had a partial mediating role between resilience and depression among nurses in a clean operating department, suggesting that hospitals should not only increase the resilience of medical staff in the face of adversity but also promote the mental health level of this group by improving their life satisfaction.

Research perspectives

Depression is not the only psychological problem that nurses in clean operating departments face. In the future, we will further study psychological distress and its influencing factors among nurses in clean operating departments to provide a more reliable theoretical basis for ensuring their mental health.

FOOTNOTES

Author contributions: Gao G and Shen XF contributed to study concepts and study design; Li L, Ma H, and Liu J contributed to data acquisition and data analysis; Jin LW, Li X, and Wang JS contributed to literature research.

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Effect of CICARE communication nursing model combined with motivational psychological intervention in patients with post-intensive care unit syndrome

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Abstract

BACKGROUND

Post-intensive care syndrome (PICS) is a term used to describe a constellation of new or worsened dysfunctions in the physical, cognitive, or mental health status of critically ill patients after their discharge from the intensive care unit (ICU). These dysfunctions persist beyond the acute phase of illness and have a significant impact on both the patient and their family. Connect, Introduce, Communicate, Ask, Respond, Exit (CICARE) communication advocates that patients should be respected and accepted when receiving medical services. Clinicians should attach importance to the communication mode of feelings, including connection, introduction, communication, ask, response, and exit 6 steps.

AIM

To assess the impact of CICARE communication on the reduction of anxiety, depression, and post-traumatic stress disorder (PTSD) symptoms in patients transitioning from the ICU to other care settings.

METHODS

This prospective, randomized, controlled study was performed between October 2021 and March 2023. Intensive Care Unit Memory Tool was used to evaluate patients' ICU memory. The Hospital Anxiety and Depression Scale was employed to determine the presence of anxiety or depression symptoms. Impact of Event Scale-Revised was utilized to assess the presence of PTSD. All data were processed and analyzed using R language software version 4.1.0. The measurement data were expressed as mean ± SD, and the *t* test was used. The count data were analyzed by the χ^2 test and expressed as [*n* (%)].

RESULTS
In total, 248 subjects were included in this study. Among them, 206 were successfully followed up for three months after transfer from the ICU, and 42 cases were lost to follow-up. There was no significant difference in the composition of ICU memory between the two groups. The application of the CICARE communication nursing model combined with the motivational psychological intervention nursing model, as well as the adoption of only the motivational psychological intervention nursing model, demonstrated favorable effects on PICS. Both groups of patients showed a reduction in anxiety scores, depression scores, and PTSD scores following the implementation of these two nursing models. However, it is noteworthy that the experimental group exhibited greater improvements compared to the control group.

CONCLUSION
Our findings suggest that CICARE communication nursing mode may have good influence on relieving PICS.

Key Words: Connect, Introduce, Communicate, Ask, Respond, Exit; Post-intensive care syndrome; Motivational psychological intervention

Core Tip: Post-intensive care syndrome (PICS) is a series of new or aggravated dysfunctions in the physical, cognitive or mental health status of a critically ill patient after discharge from intensive care unit. Connect, Introduce, Communicate, Ask, Respond, Exit (CICARE) communication advocates that patients should be respected and accepted during the provision of medical services. CICARE communication nursing mode may have good influence on relieving PICS.

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INTRODUCTION

Connect, Introduce, Communicate, Ask, Respond, Exit (CICARE) communication is an approach that emphasizes the respect, acceptance, and acknowledgement of patients during the delivery of medical services. It places importance on the effective communication of emotions, encompassing six key steps: Connect, introduce, communicate, ask, respond, and exit. Research has shown that under the clear guidance of these steps, patients' satisfaction with health care has been improving[1]. For example, the application value of CICARE communication mode nursing intervention in patients with coronary artery disease after percutaneous coronary intervention has demonstrated notable value. It has shown great potential in reducing disease uncertainty, improving treatment adherence, enhancing patients' self-care abilities, and promoting both quality of life and nursing satisfaction[2].

With the development of modern technology and medical technology, intensive care unit (ICU) treatment technology has rapid development, including advanced respiratory and circulation acquired immunodeficiency syndrome, a variety of standard diagnosis and treatment guidelines, the implementation of health education programs, so that the short-term results of ICU patients, including mortality rates and 28-d survival rates, there has been a significant increase[3]. However, the long-term prognosis and quality of life of sepsis patients remains poor, and there are many studies showings that some patients transferred out of ICU may be suffer from cognitive, mental, and physical impairments are common in patients transferred out of ICU, which can last for months or even years, or remission over time and this syndrome is called post-intensive care syndrome (PICS) which is a range of cognitive, mental, and physical impairments that are new or increased in critically ill patients after transfer from ICU and continue to affect the patient after discharge; or because of the patients admitted to ICU for treatment and late care, the family members brought a variety of pressure, resulting in psychological and physical disorders[4-7].

Numerous studies have focused on developing strategies to reduce the risk of PICS, and caregivers of PICS. High levels of education and early active mobilization are considered potential risk factors for PICS[8-11]. The impact of nursing interventions on PICS is an area that has been inadequately explored in the existing literature. Specifically, the influence of CICARE communication on PICS remains largely understudied. In light of this knowledge gap, our study aimed to evaluate the potential effects of CICARE communication on the duration of post-ICU stay, as well as its impact on anxiety, depression, and post-traumatic stress disorder (PTSD) symptoms among patients transitioning from the ICU to other care settings.

MATERIALS AND METHODS

Research contents

This prospective, randomized, controlled study was performed between October 2021 and March 2023 in Department of Neurosurgery, Dushu Lake Hospital Affiliated to Soochow University. The study was registered at the Clinical Trial Center (www.researchregistry.com) with registration number (researchregistry9376). All subjects have signed the consent form before participating in the study. Patients were divided into two groups, experiment group and controlled group. The patients of experiment group received the CICARE communication nursing model combined with motivational psychological intervention nursing model, and the patients of controlled group received the motivational psychological intervention nursing model. The main study objective was to investigate differences in the occurrence of symptoms of anxiety, depression and PTSD at 3 mo after ICU transfer between two groups of patients receiving different modes of nursing care.

Patient selection

Patients hospitalized and successfully transferred out of comprehensive ICU were selected as subjects by convenience sampling. All patients seen by the investigators in their clinical practices or who responded to requests for volunteers were screened for participation in the study. Those who met the screening criteria and gave their consent were sequentially admitted. Inclusion criteria: (1) At least 18 years old; (2) ICU stay longer than 24 h; (3) Patients transferred to the general ward after ICU treatment; and (4) Informed consent and voluntary participation in the study. Exclusion criteria: (1) Patients with severe brain injury or brain disease; (2) Patients with cognitive dysfunction; (3) Patients with language dysfunction and inability to communicate effectively; (4) Patients transferred to ICU twice or more; (5) Patients with mental disorders; and (6) Patients with malignant diseases receiving palliative care.

Materials

General information questionnaire: The general information questionnaire included gender, age, education, length of stay in ICU, diagnosis of ICU admission, presence of sepsis during ICU treatment, presence of hormones, and presence of analgesics. Intensive Care Unit Memory Tool (ICUMT): The ICUMT, assessment of patients' ICU memory, consists of a total of 14 questions: 5 open-ended questions and 9 closed questions. It mainly includes three parts: (1) The memory of admission and ICU transfer; (2) The memory during ICU care was divided into three dimensions, a total of 21 items: Factual memory (family, face, darkness, alarm sound, breathing tube, clock, sound, sputum aspiration, nasal cannula, light, medical rounds); delusional memories (others wanting to harm themselves, hallucinations, nightmares, dreams); emotional memory (discomfort, confusion, low mood, anxiety and panic, panic, pain); and (3) Memory after transfer out of ICU and ICU[12].

The Hospital Anxiety and Depression Scale (HADS): HADS was divided into two subscales of anxiety and depression, with a total of 14 items, among which 7 items (A) assessed anxiety and 7 items (D) assessed depression, and each item was scored at four levels of 0-3. The subscale was divided into critical value with 8 points, 0-7 points indicated no symptoms, and 8-10 points indicated possible anxiety or depression. A score of 11 to 21 indicates the presence of anxiety or depression symptoms, and the higher the score, the more severe the anxiety or depression symptoms[13,14].

Impact of Event Scale-Revised (IES-R): IES-R consists of 22 entries, including the three core symptoms of PTSD: Intrusion, avoidance and increased alertness were scored on five levels ranging from 0 (never) to 4 (always), with a total score ranging from 0 to 88, and a critical value of 35. The total score ≥ 35 was classified as positive PTSD symptoms, and the higher the score, the more serious the PTSD symptoms[15].

Within one week after the patients were transferred from ICU to the general ward (with appropriate extension to two weeks for special patients), the researchers visited the ward for follow-up, and reported. After knowing the purpose and significance of the study, the informed consent was signed after obtaining the informed consent of the patients, and the general information questionnaire and ICU memory assessment scale were distributed. For the patients who could not complete the questionnaire independently, the questionnaire contents were read aloud word by word, and the patients provided oral answers, and the researchers filled in the answers for them. HADS and IES-Rs were collected by telephone interview at 3 mo after patients were transferred out of the ICU. The questionnaire was read aloud, word for word, and the patients responded verbally, while the researchers wrote the answers for them. Limit each phone interview to 15 to 20 min.

Statistical analyses

The integrity of all questionnaires was checked before input, and invalid questionnaires with obvious logical contradictions or too many missing items were eliminated. All data were processed and analyzed using R language software version 4.1.0. The measurement data were expressed as mean ± SD, and the t test was used. The count data were expressed as [n (%)], and the χ^2 test was used. $P < 0.05$ was considered statistically significant.

RESULTS

There were 248 subjects were included in this study, and 206 patients were successfully followed up three months after being transferred out of ICU, and 42 cases were lost to follow-up from October 2021 and March 2023. The reasons for the loss of follow-up included death, refusal to participate in the investigation, loss of contact, and failure to cooperate with

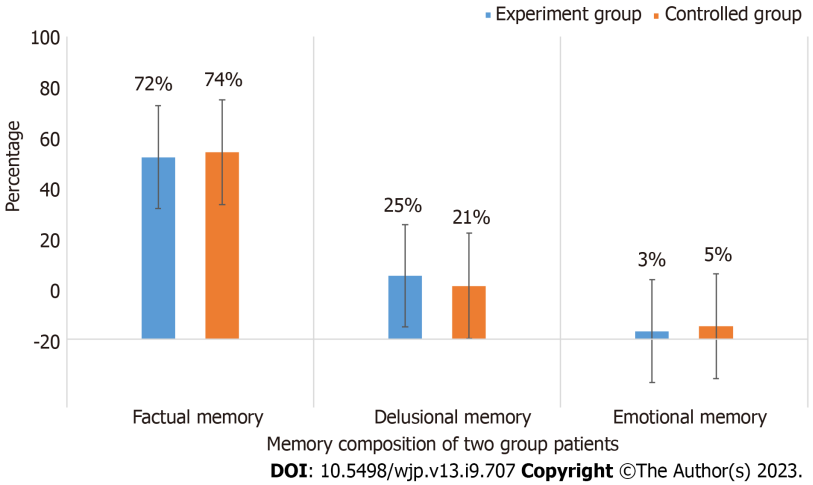

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Figure 1 Intensive care unit memory composition of two group patients.

the investigation in critical condition. Among 206 patients successfully followed up, 125 (60.7%) were male and female in 81 cases (39.3%); most of the patients were over 45 years old, with 112 cases (54.4%), which were presented in Table 1.

There was no statistical difference in the composition of ICU memory between the two groups, and 72% of patients in the experimental group had factual memory. Delusional memory was present in 25% of patients and emotional memory was present in 3%; in the control group, 74% of patients had factual memories, 21% had delusional memories, and 5% had emotional memories (see Figure 1). There was no statistic difference in ICU memory composition of two group patients.

HADS and IES-R score change of two group patients were presented in Table 2. Adopting CICARE communication nursing model combined with motivational psychological intervention nursing model and only adopting motivational psychological intervention nursing model both had good influence on PICS. Anxiety score, depression score and PTSD score of both group patients decreased after using these two nursing modes, but experiment group was better than the control group.

DISCUSSION

Annually, a staggering number of over 20 million patients worldwide necessitate ICU treatment due to severe illness, injury, or the worsening of chronic conditions. Advances in medical technology have increased the survival of critical illness, increasing the number of patients transferred out of the ICU, and increasing attention to their long-term outcomes [16,17]. Patients may experience both physiological and psychological stressors during their stay in the ICU, including critical illness, sedation, pain, sleep deprivation, noise, delirium, lack of privacy, and fear. These experiences can significantly impede the recovery process and may even contribute to the development of psychological disorders, including anxiety, depression, and PTSD, following the patient's discharge from the ICU. Among these, anxiety, depression, and PTSD are the most prevalent psychological conditions observed in such cases[18]. According to the above facts, The American Academy of Critical Care Medicine Put forward the concept of PICS that it is a series of new or aggravated dysfunction in the physical, cognitive or mental health status of a critically ill patient after discharge, which continues to affect the patient or his or her family. There are many studies on the influencing factors of psychological disorders in patients transferred out of ICU, mainly focusing on demographic factors (such as gender, age, education level, family income, *etc.*), disease factors (such as chronic history, severity of disease, sepsis, *etc.*), and factors related to ICU treatment (such as the use of glucocorticoids, the use of analgesics, the use of sedatives, *etc.*). It is a great challenge for intensive care to improve long-term mental health and health-related quality of life of patients transferred out of ICU.

CICARE communication mode is a process-oriented communication approach advocated by American medical institutions. It integrates psychological and medical knowledge along with humanistic values to enhance the effectiveness of communication between healthcare providers and patients in outpatient settings. The implementation of CICARE communication mode aims to improve patients' medical experience and enhance the overall quality of care delivery. In our study, 14 nurses were trained in CICARE communication mode for 1 mo and passed the examination. CICARE mode was fully applied in the experiment group patients who accepted the motivational psychological intervention at same time. After study and observation, the experiment patients more willing to speak out their demand and worries. Other studies have found the same thing[2,19-21]. CICARE communication is a mode of communication that advocates good communication that attends to the patients feelings of being respected, accepted and valued during the provision of medical services for patients, including connect, introduce, communication, ask, response and exit. Patients feel respected and are more likely to trust their doctors, talk about their problems, and give feedback. A major limitation of this study is that we enrolled a small sample size from a single-center study. Therefore, our results may not be generalized.

Table 1 Baseline characteristics of subjects

	Indicator	Number	Percentage
Gender	Male	125	60.7
	Female	81	39.3
Age (yr)	< 30	27	13.1
	30-45	67	32.5
	> 45	112	54.4
Operation situation	Non-operation	38	18.4
	Elective operation	102	49.5
	Emergency	66	32.1
Length of ICU stay	1-5	123	59.7
	5-10	55	26.7
	10-20	14	6.8
	> 20	14	6.8
Tranquilizer	Yes	181	87.9
	No	25	12.1
Sedative	Yes	166	80.6
	No	40	19.4

ICU: Intensive care unit.

Table 2 Hospital Anxiety and Depression Scale and Impact of Event Scale-Revised score change of two group patients

	Experiment group	Controlled group
Samples	103	103
Anxiety score	12	11
Depression score	10	9
PTSD score	52	52
ICU transfer anxiety score at three months	3	6
Depression score at three months after ICU transfer	2	5
PTSD score at three months after ICU transfer	16	38

PTSD: Post-traumatic stress disorder; ICU: Intensive care unit.

CONCLUSION

CICARE communication nursing mode may have good influence on relieving PICS. Patients transferred from ICU can be adopted CICARE communication nursing model combined with motivational psychological intervention nursing model, rather than only motivational psychological intervention nursing model.

ARTICLE HIGHLIGHTS

Research background

Connect, Introduce, Communicate, Ask, Respond, Exit (CICARE) communication is a kind of advocating that patients should be respected, accepted and accepted when providing medical services attach importance to the communication mode of feelings. Post-intensive care syndrome (PICS) is a series of new or aggravated dysfunction in the physical, cognitive or mental health status of a critically ill patient after discharge, which continues to affect the patient or his or her family.

Research motivation

The aim of this study was to evaluate CICARE communication whether shorten post-intensive care (ICU), affecting anxiety, depression, and post-traumatic stress disorder (PTSD) in patients transferred out of the ICU.

Research objectives

The object of this study as follows: (1) Assess the impact of CICARE communication combined with motivational intervention on anxiety, depression, and PTSD symptoms in PICS patients; (2) Compare outcomes between CICARE + motivational intervention and motivational intervention alone; and (3) Determine feasibility and acceptability of implementing CICARE communication in PICS care.

Research methods

The study employed a prospective, randomized, controlled design. Data collection occurred from October 2021 to March 2023. ICU memory was evaluated using the Intensive Care Unit Memory Tool. Anxiety and depression symptoms were assessed using Hospital Anxiety and Depression Scale, while PTSD was measured with Impact of Event Scale-Revised. Statistical analysis utilized R software (version 4.1.0). Follow-up was conducted for three months after ICU transfer.

Research results

There was no statistical difference in the composition of ICU memory between the two groups. Adopting CICARE communication nursing model combined with motivational psychological intervention nursing model and only adopting motivational psychological intervention nursing model both had good influence on PICS. Anxiety score, depression score and PTSD score of both group patients decreased after using these two nursing modes, but experiment group was better than the control group.

Research conclusions

CICARE communication nursing mode may have good influence on relieving PICS.

Research perspectives

Patients transferred from ICU can be adopted CICARE communication nursing model combined with motivational psychological intervention nursing model, rather than only motivational psychological intervention nursing model.

FOOTNOTES

Author contributions: She SJ and Xu YY contributed equally to this work; Xu YY designed the study; She SJ contributed to the analysis of the manuscript; She SJ and Xu YY involved in the data and writing of this article; and all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Dushu Lake Hospital Affiliated to Soochow University Institutional Review Board.

Clinical trial registration statement: The study was registered at the Clinical Trial Center (www.researchregistry.com) with registration number (researchregistry9376).

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