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REVIEW

Role of adjunctive nonpharmacological strategies for treatment of rapid-cycling bipolar disorder

Subho Chakrabarti, Amal J Jolly, Pranshu Singh, Nidhi Yadhav

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Abstract

Rapid-cycling bipolar disorder (RCBD) is a phase of bipolar disorder defined by the presence of ≥ 4 mood episodes in a year. It is a common phenomenon characterized by greater severity, a predominance of depression, higher levels of disability, and poorer overall outcomes. It is resistant to treatment by conventional pharmacotherapy. The existing literature underlines the scarcity of evidence and the gaps in knowledge about the optimal treatment strategies for RCBD. However, most reviews have considered only pharmacological treatment options for RCBD. Given the treatment-refractory nature of RCBD, nonpharmacological interventions could augment medications but have not been adequately examined. This review carried out an updated and comprehensive search for evidence regarding the role of nonpharmacological therapies as adjuncts to medications in RCBD. We identified 83 reviews and meta-analyses concerning the treatment of RCBD. Additionally, we found 42 reports on adjunctive nonpharmacological treatments in RCBD. Most of the evidence favoured concomitant electroconvulsive therapy as an acute and maintenance treatment. There was preliminary evidence to suggest that chronotherapeutic treatments can provide better outcomes when combined with medications. The research on adjunctive psychotherapy was particularly scarce but suggested that psychoeducation, cognitive behavioural therapy, family interventions, and supportive psychotherapy may be helpful. The overall quality of evidence was poor and suffered from several methodological shortcomings. There is a need for more methodologically sound research in this area, although clinicians can use the existing evidence to select and individualize nonpharmacological treatment options for better management of RCBD. Patient summaries are included to highlight some of the issues

concerning the implementation of adjunctive nonpharmacological treatments.

Key Words: Rapid-cycling bipolar disorder; Bipolar disorder; Adjunctive therapy; Nonpharmacological treatment

Core tip: Rapid-cycling bipolar disorder (RCBD) is a common and highly disabling phase of bipolar disorder. The ineffectiveness of conventional pharmacological treatment for RCBD suggests that adjunctive nonpharmacological interventions could be useful. However, their role has not received much attention. This review carried out a comprehensive search to identify the existing evidence on the subject. We found that electroconvulsive therapy, chronotherapy, and psychotherapy could effectively augment medication treatment of RCBD. However, the evidence is limited and methodologically inadequate. Therefore, clinicians have to rely on general guidelines for the optimal use of the available nonpharmacological options while managing RCBD.

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INTRODUCTION

Clinical features of rapid-cycling bipolar disorder

Rapid-cycling bipolar disorder (RCBD) is a phase in the longitudinal course of BD characterized by increased episode frequency. The Diagnostic and Statistical Manual of Mental Disorders (DSM) delineates rapid cycling as a specifier of the longitudinal course of BD rather than a distinct form of the disorder[1]. DSM-5 defines rapid cycling as a minimum of four episodes in the previous 12 mo that meet the diagnostic and duration criteria for hypomanic, manic, or major depressive episodes. Each episode is demarcated by either partial or full remission for at least 2 mo, or a switch to a new episode of the opposite polarity. A proportion of patients have shorter cycles of days to weeks (ultra-RCBD) and some have episodes lasting less than a day (ultradian-RCBD)[2-6]. However, DSM-5 does not include these categories.

The phenomenon of rapid cycling occurs among a significant proportion of patients with BD. The 12-mo prevalence of RCBD in patients from specialized mood disorder clinics is about 20% (range: 4%–27%)[4,6-9]. The prevalence is higher (range: 27%–56%) when ultrarapid and ultradian rapid cycling are included[6,7,10,11]. The rates are also higher in community settings (30%–40%) because these studies have included a wide spectrum of RCBD[9,12-14]. Reviews have estimated the annual prevalence rate of RCBD to be about 18% (range: 5%–33%) and lifetime rates of about 31% (range: 26%–43%)[9,15-18]. The rates obtained by different meta-analytic studies also vary from 15% to 24% (range: 12%–56%)[5,19-21].

Apart from its frequent occurrence, RCBD is characterized by clinical features that make it a severe and disabling phenomenon. Depressive episodes or symptoms appear to be the characteristic clinical presentation of RCBD[5,10,15,17,22]. Patients with BD who have depressive onsets are more likely to develop rapid cycling and patients with RCBD are more likely to present with depressive onsets. Episodes of depression are more frequent and severe in patients with RCBD. Depressive episodes are harder to treat compared with manic ones. As a result of this greater depressive burden, most reviews have also found a higher rate of suicidality in RCBD[5,16,21,23,24]. The frequent recurrence of treatment-resistant depression contributes to the treatment-refractory profile of RCBD. The distress and disability associated with unremitting depression are the main hurdles in effectively managing RCBD[10,13,14,22,25]. Although RCBD is a transient phenomenon that lasts about 2 years in most patients[2,6,16,22,24], many studies have found rapid cycling to persist in > 50% of patients[6,25-28]. A longer duration of rapid cycling, more frequent episodes, a depression-mania-free interval pattern, continuous cycling, agitated depression, temperamental disturbances, and poor response to treatment are associated with the persistence of RCBD[6,8,17,29,30]. Lastly, the consistent finding in the literature is that RCBD is associated with poorer outcomes in terms of severity, recurrence risk, chronicity, comorbidity, and treatment resistance [17-20,31]. Given all these adverse clinical features, it is not surprising that RCBD is associated with greater global functional impairment, poor socio-occupational outcomes, higher levels of disability, poorer quality of life, and greater family burden[2,6,9,16,24]. Thus, RCBD adds a great deal to the overall burden of BD[18].

Pharmacotherapy of RCBD

Since pharmacotherapy is the principal means of treating BD, the primary focus of research has been on the efficacy of medications in RCBD. Several reviews of the subject exist in the current literature. These include narrative reviews[4,24,27,30,32], systematic reviews[6,16,17,29,31], and meta-analyses[5,18,20,21,33] (Supplementary Material includes a complete list of all the reviews consulted).

The main finding of this research is that RCBD is resistant to treatment by conventional pharmacotherapy for BD[6,20,27,29,30]. RCBD comprises the largest group among patients with treatment-resistant BD[34]. Patients with RCBD have poorer treatment response and outcome compared to patients without rapid cycling[26,27,29,30,35]. Although initial studies suggested that RCBD responds poorly to lithium, it is now clear that rapid cycling is resistant to all mood-stabilizing treatments[6,20,36-38]. Treating depressive episodes in RCBD poses greater problems than treating mania/hypomania. The acute efficacy of medications is usually better than their long-term effects[8,11,18,29,32]. Recommendations regarding effective treatment options vary, but most of the evidence appears to favour second-generation antipsychotics, lithium, valproate, lamotrigine, thyroxine, and even antidepressants[17,18,24,31,39]. There is a considerable consensus that response to monotherapy is often inadequate. Therefore, combinations of mood stabilizers and antipsychotics are the more practical, if not the evidence-based options for treatment[17,40-43]. However, the prevailing concern about medication treatments for RCBD is the lack of research data and guidance on suitable evidence-based options, particularly for long-term treatment[17,18,24,29,31]. Not only is there a lack of randomized controlled trials (RCTs) on the subject, but there are also several methodological lacunae such as small sample sizes, uncertainties about the definition of RCBD, and inadequate study designs[6,11,18,20,44].

Nonpharmacological therapy for RCBD

The shortcomings of pharmacological treatment indicate an unmet need for more effective management options for RCBD. Adjunctive nonpharmacological interventions could fill the existing gap in managing RCBD[18,36,45-47]. Treatments such as electroconvulsive therapy (ECT), chronotherapy, and psychotherapy can potentially augment the inadequate response obtained with medications. However, the role of adjunctive nonpharmacological treatments has not received much attention. A systematic review conducted in 2007 considered the different biological and psychotherapeutic options that could augment the pharmacological treatment of RCBD[45]. It found some evidence for the efficacy of ECT and sleep deprivation for acute and maintenance management of RCBD, especially in treatment-resistant patients. Light therapy was not efficacious and there was no data on recurrent transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and psychotherapeutic treatments. The authors acknowledged that the evidence was based only on case reports and open trials and not RCTs. However, they concluded that adjunctive nonpharmacological treatments could be used to manage RCBD based on clinical experience and their usefulness in BD. They recommended the early institution of adjunctive treatments such as ECT in patients who were severely ill and needed immediate relief. Subsequent reviews of the treatment of RCBD have also noted the potential for concomitant use of nonpharmacological treatments and the lack of controlled trials in this area[17,18,32,46,47].

There are several reasons for examining the role of combined pharmacological and nonpharmacological therapy in RCBD. At present, there is no consensus or guidance on the optimal management of RCBD because pharmacological and nonpharmacological treatments have proved less effective[17,18,25,45]. Apart from the inadequate response to standard pharmacotherapy, many other factors make rapid cycling difficult to treat. These include its high prevalence, greater severity, depressive colouring, comorbidities, poorer outcomes, higher levels of disability, side-effect burden, and inadequate medication adherence[15,17,18,24,36]. Adjunctive nonpharmacological treatments can address some of these issues such as persistent depressive symptoms and risks of harm[45], comorbidities[2,10,40], psychosocial stressors, functional impairment[25,32,48-50], and treatment nonadherence[25,30,45,51,52].

Aims of this review

This review aimed to summarize the existing evidence on the role of nonpharmacological therapies as adjuncts to medications in RCBD. It attempted to expand on the previous review[45] by conducting a more comprehensive and updated search of this area.

LITERATURE REVIEW

Although this was not a systematic review, it relied on comprehensive electronic (PubMed) and manual searches to identify the existing literature on nonpharmacological treatments in RCBD from 1980 to April 2023. The accompanying figure depicts this search. Supplementary Material includes the details of the search terms used. The Reference Citation Analysis tool was used for searching articles and ranking them according to their impact (Figure 1).

This search identified 53 narrative reviews, 21 systematic reviews, and nine meta-analyses on the treatment of RCBD. These reviews were used to collate information regarding various nonpharmacological therapies in RCBD. A second round of electronic and manual searches identified 17 studies or reports of ECT, 16 of chronotherapy, six of psychotherapy, two of VNS, and one of rTMS. Patients consented to the presentation of their treatment histories. All patient details have been anonymized.

RESULTS

Adjunctive ECT in RCBD

ECT has proven efficacy in BD in treating acute episodes of both mania and depression. It is particularly useful in medication-resistant episodes that are severe, psychotic, or with a high risk of self-harm. The evidence also suggests that maintenance ECT in combination with medication is efficacious for patients with highly recurrent illnesses if they have

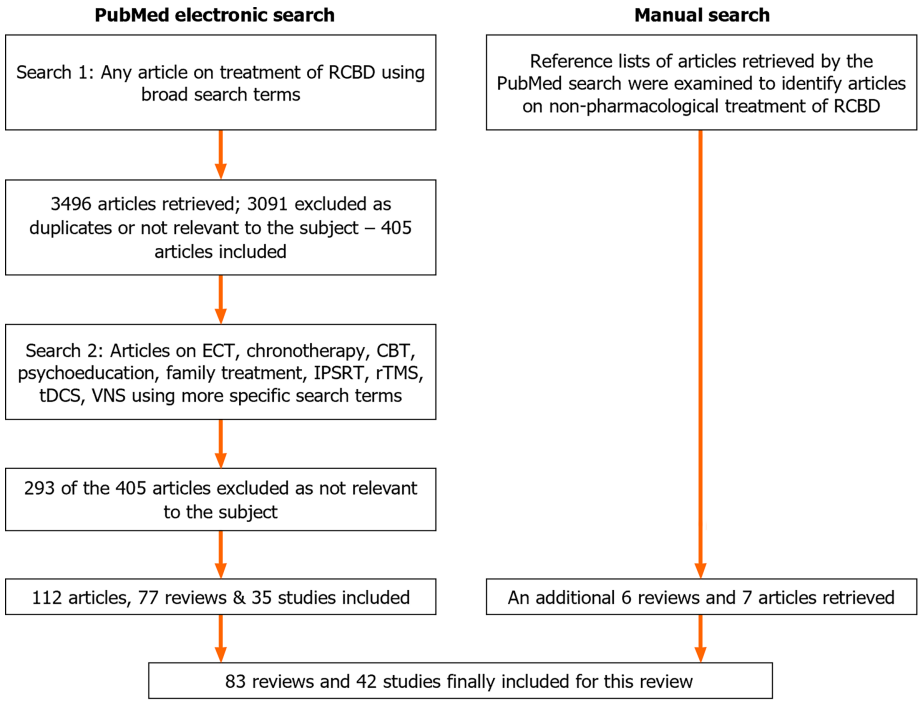

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Figure 1 Search strategy for identifying articles on nonpharmacological treatment of rapid cycling bipolar disorder. Search terms are listed in (Supplementary Material). CBT: Cognitive behavioural therapy; IPSRT: Interpersonal and social rhythm therapy; RCBD: Rapid-cycling bipolar disorder; rTMS: Recurrent transcranial magnetic stimulation; tDCS: Transcranial direct current stimulation; VNS: Vagus nerve stimulation; ECT: Electroconvulsive therapy.

responded well to acute ECT[3,45,53-55]. Consequently, ECT has been used for similar indications in patients with RCBD. However, the evidence is limited and based on either case reports or naturalistic studies with small numbers of patients. These studies are included in Table 1[56-72].

Despite these limitations, acute ECT seems to be effective in patients with medication-resistant RCBD with complete or partial remission rates ranging from 70% to 100% in some studies[69,72]. Others have reported lower response rates[64,66,67,70]. Nevertheless, sustained periods of remission and better response to mood stabilizers are reported after acute ECT[64,65,67,70,72]. Acute ECT also reduces the number of episodes and the time spent ill. Though there are fewer studies, the combination of maintenance ECT and mood stabilizers appears to be effective with response rates ranging from 67% to 100%[68,70,71]. Adjunctive maintenance ECT prevents relapses, reduces the need for hospitalization and the length of hospital stay, decreases the time spent in episodes, and increases the duration of interepisodic intervals[68,70,71,73,74]. Patients with RCBD and ultra-RCBD may respond better to ECT than other patients with BD[41,45]. ECT is particularly helpful in patients with RCBD who have failed multiple medication trials, those who are intolerant to medication side effects, and those who are at high risk of self-harm[3,45,49]. ECT is effective in medication-resistant patients with mania[3,30,47,75,76], depression[32,41,68,72,75], or mixed states[49,72] as a part of RCBD. However, the best response is often obtained in patients with bipolar depression[32,41,67,68,72]. Other predictors of good response are depressive episodes with psychotic symptoms or catatonic features[41,68,72]. Minnai *et al*[71] carried out a multivariate analysis to identify the predictors of good response to maintenance ECT in RCBD. Young age, male sex, type II BD, and hyperthymic temperament emerged as factors associated with a higher chance of depression-free intervals with ECT. The better response in those with type II BD and hyperthymic temperament could be because a large proportion of these patients were included in their sample. However, hyperthymic temperament is often associated with antidepressant-induced rapid cycling[6], while ECT may be less likely to cause rapid cycling than antidepressants[4]. The use of ECT has shown to be safe with minimal side effects even when it is combined with mood stabilizers and used for long periods[62,63,68,71,72]. ECT is also less likely than antidepressants to cause manic/hypomanic switches or induce rapid cycling[4,48,49,64,76].

Thus, despite the scarcity of evidence, acute ECT is recommended for treating medication-refractory manic and depressive episodes in RCBD[30,32,45,49,76]. Maintenance ECT can be considered in those patients who improve with acute ECT or relapse on pharmacotherapy[45,73-77]. ECT is more effective if started early in the course of treatment because the outcome is likely to be worse if it is delayed[45,69].

Two of our patients (numbers 1 and 2) received acute ECT with varying degrees of success (Supplementary Material).

Adjunctive ECT in RCBD patient examples

A 72-year-old man with medication-resistant RCBD received two courses of acute ECT in 2017 for episodes of severe depression. The response to the first course was good with complete remission from depression. However, he did not respond as well with the second course a few months later. The depressive episodes did not remit and his rapid cycling continued. He had physical complications during ECT and was unwilling to try ECT further. Later, his rapid cycling

Table 1 Studies of adjunctive electroconvulsive therapy in rapid-cycling bipolar disorder

Ref.	Sample	Results
Case reports		
Berman and Wolpert[56], 1987	18-yr-old woman with medication-resistant RCBD	ECT during mania led to complete remission, which was maintained for 14 mo without medications
Mizukawa *et al* [57], 1991	81-yr-old woman with medication-resistant ultra-RCBD	ECT did not prevent the recurrence of episodes over a period of 35 yr of observation
Benjamin and Zohar[58], 1992	45-yr-old man with treatment-resistant RCBD	Depressive episodes responded transiently to total sleep deprivation and psychotherapy but complete remission was only achieved with acute ECT
Kho[59], 2002	79-yr-old woman with medication-resistant RCBD	ECT and lithium was used successfully during acute and maintenance treatment
Zavorotnyy *et al* [60], 2009	63-yr-old woman with medication-resistant bipolar disorder	The patient developed ultra-rapid cycling during acute ECT, which responded to the continuation of ECT and addition of lithium
Amino *et al*[61], 2011	63-yr-old woman with medication-resistant RCBD	Continuation-ECT for 12 mo prevented rehospitalization
Huber and Burke [62], 2015	67-year-old woman with medication-resistant ultra-RCBD	ECT was used to successfully treat depression and manic episodes that developed on discontinuation of lithium
Kranaster *et al*[63], 2017	21-yr-old woman with medication-resistant ultra-RCBD	ECT was used to successfully treat a treatment-resistant depressive episode
Observational studies		
Kukopulos *et al* [64], 1980	87 patients with RCBD	11 patients treated only with ECT for 7–35 yr remained in remission for long periods
Kukopulos *et al* [65], 1983	87 patients with RCBD	ECT was more effective than antidepressants in treating severe depression and when combined with lithium led to longer remissions
Wehr *et al*[66], 1988	24 patients with medication-resistant RCBD	None of the patients remitted with ECT
Mosolov and Moshchevitin[67], 1990	8 patients with mood stabilizer-resistant RCBD	Acute ECT lead to remission for 6 mo in 3 patients. The number of episodes and the time spent in mood episodes was reduced. Mood stabilizers were more effective following acute ECT treatment
Vanelle *et al*[68], 1994	Four patients with medication-resistant RCBD	Maintenance ECT for 18 mo led to full or partial remission in all 4 patients. Time spent in the hospital was reduced. Response was better in depressive episodes with psychotic symptoms
Wolpert *et al*[69], 2013	Six patients with continuous cycling	ECT started early in the course of cycling was effective in reducing recurrences
Koukopoulos *et al* [70], 2003	43 patients of RCBD who received ECT	11 patients remitted with ECT and mood stabilizer combinations and maintained in this state for 2–36 yr. Temporary improvement was noted in the others. Two out of 3 patients on maintenance ECT had good response
Minnai *et al*[71], 2011	14 patients with medication-resistant RCBD treated with maintenance ECT. Comparisons of 2-yr periods before and after ECT	All patients improved. Eight did not relapse over 2 yr and 6 had only one episode annually. Time spent ill was reduced and interepisodic periods were longer. Young males with type II BD and hyperthymic temperament had better outcome
Mosolov *et al*[72], 2021	1-year prospective study of 30 patients with RCBD and ultra RCBD with poor response to mood stabilizer treatment. Comparisons of 1-yr periods before and after acute ECT	40% achieved and maintained remission with ECT and lithium treatment; 30% showed partial response with the combination and 30% did not respond. Duration of mood episodes was significantly reduced with ECT. Mixed depression with/without catatonia had better response to acute ECT

ECT: Electroconvulsive therapy; RCBD: Rapid-cycling bipolar disorder; type II BD: Bipolar disorder type II; Ultra-RCBD: Ultra-rapid-cycling with shorter cycles of days to weeks; Ultradian-RCBD: Ultradian rapid-cycling with episodes lasting less than a day.

responded to repeated administration of partial sleep deprivation during depressive episodes and dark therapy during hypomanic episodes. A 42-year-old woman with medication-resistant, ultra-rapid, and ultradian cycling was administered ECT in 2005 during an episode of psychotic depression with high suicidal risk. She improved but her cycling did not stop. She was administered ECT again in 2015 for a mixed episode with psychosis and suicidal risk. Response to ECT was inadequate on this occasion and she had physical complications during ECT. Since then, her rapid-cycling pattern has shown a better response to intensive psychotherapy combined with medication. The detailed treatment histories of these patients (Supplementary Material) illustrate some of the disadvantages of ECT in RCBD including the variable response, greater acute than maintenance effects, and the higher risk of adverse effects in some patients[32,45,55,75]. Although ECT is used more commonly in RCBD than in the non-rapid-cycling group, it is still underutilized in RCBD because of these concerns[78,79].

Other neurostimulatory treatments in RCBD

There are few reports of rTMS and VNS treatment in RCBD. A case report described a 60-year-old woman with medication-resistant RCBD who improved after acute administration of rTMS and remained in remission for 6 mo with maintenance rTMS[80]. Another report of a 60-year-old woman with RCBD found that 12 mo of treatment with VNS reduced the severity of her depressive symptoms and the duration of her depressive episodes[81]. Finally, nine patients with treatment-resistant RCBD were treated with VNS for 1 year in a pilot study[82]. They had significant improvements in overall illness severity, the severity of depressive symptoms, and functioning. The VNS treatment was well-tolerated.

Adjunctive chronotherapy in RCBD

Chronotherapy refers to treatment based on controlled exposure to environmental stimuli such as light to alter circadian rhythms or manipulation of the sleep–wake cycle to benefit patients with psychiatric disorders[83-87]. Chronotherapy includes bright light therapy (BLT), wake therapy (total or partial sleep deprivation in the second half of the night), phase-advance of the sleep–wake cycle, triple chronotherapy (combinations of wake therapy, BLT, and sleep phase-advance) dark therapy, blue-light-blocking sunglasses, interpersonal and social rhythm therapy (IPSRT), cognitive behavioural therapy (CBT) for insomnia, and exogenously administered melatonin[84,86,88,89]. These treatments are effective among patients with BD.

Among the various options, BLT appears to be the one best supported by the evidence[86,89]. Several meta-analyses have shown medium to large effects of BLT during acute treatment of bipolar depression[89-93]. It is effective in seasonal and nonseasonal depression[94-98]. Adding BLT to antidepressants or sleep deprivation treatment yields a better response[90,99]. BLT is well tolerated and the risk of manic switches is not increased with it[93,100-103]. However, the efficacy of BLT is based on few RCTs and some meta-analyses have found no conclusive evidence for its efficacy[100,102,103].

The evidence for total or partial sleep deprivation is less convincing. Although 50%–60% of patients respond to a single session of wake therapy, the positive effects of wake therapy are usually transient[86,89,104,105]. The evidence base consists mainly of uncontrolled trials. Moreover, there may be a higher risk of manic switches. Nevertheless, several meta-analyses have concluded that wake therapy combined with medications causes significant reductions in symptoms of bipolar depression[106-109]. Combining sleep deprivation with antidepressants or mood stabilizers, BLT, or sleep phase-advance treatment also sustains its effects[107,110-112]. The treatment might be particularly effective for those with bipolar rather than unipolar depression[113-117]. There is no difference in efficacy between total and partial sleep deprivation[106,108,118,119]. Lastly, the rates of manic switches are low, except in patients with RCBD[104,107,112].

Triple chronotherapy is a treatment regimen designed to prevent the early relapse of symptoms with wake therapy [110,112,116]. It consists of one or more nights of wake therapy, followed by morning administration of BLT, and 3–5 d of sleep phase advance[84]. A systematic review[87] and a meta-analysis[120] showed that triple chronotherapy was effective in bipolar depression. Response rates ranged from 33% to 62% and the effects lasted several weeks. It was not associated with adverse effects and the rates of switching were low.

Dark therapy involves keeping patients with mania/hypomania in dark rooms for extended periods of rest and sleep [84]. This treatment can reduce manic symptoms but has not been examined in RCTs[84,86,117]. A more practical option is the use of glasses that block blue light. This treatment reduced manic and depressive symptoms and improved sleep efficiency in two RCTs[121,122].

A few RCTs of IPSRT have shown positive effects on bipolar depression during acute and maintenance treatment and a single RCT showed that CBT for insomnia improves sleep and decreases depressive symptoms[86,89].

RCBD is the prototypical example of the link between mood disorders and abnormalities of the circadian system and the sleep–wake cycle[28,123-126]. Compared to patients without rapid cycling, the circadian rhythm system in patients with RCBD is more vulnerable to the effects of environmental stimuli, for example, light and dark, irregular sleep patterns and sleep loss, and changes in the social environment such as stressful life circumstances[3,54,55,124,125]. Disturbances in circadian rhythms[3,28,124,126] and social rhythms[28,45,55,127], abnormalities of circadian genes[46,85,128,129], evening chronotypes[125,130], and hormonal abnormalities occur at a higher rate in RCBD[46,85]. However, despite this knowledge and the evidence for the efficacy of chronotherapy in BD, chronotherapy of RCBD is still an evolving area[86]. Since most of the RCTs of chronotherapy in BD usually exclude patients with RCBD, the current evidence is limited to case reports and observational studies with small sample sizes. Table 2 includes these studies and reports of chronotherapy of RCBD[58,70,127,131-143].

Despite the limited evidence, treatments such as wake therapy, BLT, dark therapy, and triple chronotherapy have been used successfully in the acute and maintenance treatment of patients with RCBD. Chronotherapy combined with medications is effective even in patients resistant to medications, ECT, or psychotherapy. There is some concern about the adverse effects of these treatments, particularly the risk of manic/hypomanic switches and exacerbation of rapid cycling with wake therapy. Early studies reported higher rates of switching with wake therapy in RCBD[110,113,114,118,119]. However, these studies mostly used total sleep deprivation. Recent studies of partial sleep deprivation have reported lower rates[115]. Moreover, the high rates are based on a small number of patients with RCBD and the rate of treatment-induced switches is probably no different from the rate of spontaneous switches in RCBD[86,115]. Lastly, such switches can be easily treated or prevented by combining sleep deprivation with medications, BLT, and phase-advance treatment [110,112,115].

Adjunctive chronotherapy in RCBD: patient examples

Four of our patients have been treated successfully with adjunctive chronotherapy. Triple chronotherapy, dark therapy, and blue-light-blocking glasses were used successfully in two inpatients: (1) A 69-year-old woman with a long history of ultra-rapid RCBD was hospitalized after 6 years of unsuccessful treatment with different combinations of medication.

Table 2 Studies of adjunctive chronotherapy in rapid-cycling bipolar disorder

Ref.	Sample	Results
Case reports		
Christodoulou *et al* [131], 1978	26-yr-old woman with rapid-cycling episodes of severe recurrent depression resistant to medications	Inpatient and outpatient total sleep deprivation every week for 36 wk led to remission for a period of 10 mo. The patient committed suicide after stopping the maintenance sleep deprivation treatments
Lovett Doust and Christie[132], 1980	48-yr-old woman with medication-resistant RCBD	Five nights of total sleep deprivation combined with medications during depressive episodes for 8 mo led to reduction in intensity and duration of depression. Switches into hypomania were recorded
Churchill and Dilsaver[133], 1990	47-yr-old woman with rapid-cycling episodes of severe recurrent depression	Partial sleep deprivation on alternate nights combined with an antidepressant led to complete remission from depression for 6 wk
Benjamin and Zohar[58], 1992	45-yr-old man with treatment-resistant RCBD resistant to antidepressants	One night of sleep deprivation was successful in aborting depressive episodes, but led to prolonged hypomania on one occasion and did not prevent the rapid-cycling pattern
Gann *et al*[134], 1993	64-yr-old man with ultradian-RCBD	Total sleep deprivation for 3 nights led to reduction of depressive symptoms for 2 wk. Further improvement occurred with carbamazepine
Eagles[135], 1994	50-yr-old man with medication-resistant ultradian-RCBD	Daily morning BLT for 2 mo produced sustained remission without hypomanic switches
Kusumi *et al*[136], 1995	2 patients with medication-resistant RCBD and nonseasonal depressions	Morning BLT led to improvement in sleep and mood. Withdrawal of BLT did not result in relapse. Remission was maintained for several months
Wehr *et al*[137], 1998	51-yr-old man with medication-resistant RCBD treated with 10–14 h of darkness, rest, and sleep over 1.5 yr	Dark therapy helped in stabilizing sleep, reducing hypomanic symptoms, and attenuating rapid cycling for the period of treatment. Lower doses of antipsychotics were required and hospital stay was shorter
Wirz-Justice *et al* [138], 1999	70-yr-old woman with medication-resistant ultra-RCBD	Rapid-cycling ceased on initiation of 10–14 h of darkness, rest, and sleep. Depression improved with mid-day BLT and remission was achieved with morning BLT. Patient remained on valproate and was stable for a year
Leibenluft and Suppes[127], 1999	42-yr-old woman with medication resistant ultra-RCBD	A lifestyle intervention that ensured a regular sleep–wake schedule in combination with medications led to decrease in rapid cycling
Observational studies		
Papadimitriou *et al* [139], 1981	5 patients with treatment-resistant RCBD	Weekly regimens of total sleep deprivation administered over several months reduced relapses and increased the duration of remissions
Wehr *et al*[140], 1982	9 patients with RCBD treated with 1 night of total sleep deprivation during depressive episodes	Depressive symptoms improved in 8 patients with sleep deprivation but 7 developed mania or hypomania
Papadimitriou *et al* [141], 1993	5 medication-free patients with RCBD treated with total sleep deprivation twice a week for 4 wk	All 5 patients responded to sleep deprivation treatment with > 50% improvement in depressive symptoms and remained in remission for a year with weekly sleep deprivation treatments. Rapid-cycling, young age, female sex, family history of mood disorder and illness duration < 10 yr predicted response. Hypomania was observed in 1 patient
Gill *et al*[142], 1993	3 patients with treatment-resistant RCBD treated with total sleep deprivation and mood stabilizers and antidepressants	Duration of response was significantly better when sleep deprivation treatment was administered late rather than early in the depressive episodes
Leibenluft *et al* [143], 1995	9 patients with RCBD treated with 3 mo of BLT and medications versus 3 mo of only medication treatment	Mid-day BLT was more effective in reducing depressive symptoms and days spent depressed than morning or evening BLT. Morning BLT precipitated hypomanic switches
Koukopoulos *et al* [70], 2003	2 women with RCBD	Sleep deprivation resulted in a temporary improvement of depression

BLT: Bright light therapy; RCBD: Rapid-cycling bipolar disorder; Ultra-RCBD: Ultra-rapid-cycling with shorter cycles of days to weeks; Ultradian-RCBD: Ultradian rapid-cycling with episodes lasting less than a day; Partial sleep deprivation: Sleep deprivation during the second half of the night; Total sleep deprivation: Sleep deprivation for 36 h.

Hypomania at admission responded well to dark therapy within 3–4 d and her antipsychotics could be stopped. She was started on triple chronotherapy when her depressive symptoms began to reappear 2 wk later. With two courses of this treatment, she remitted completely and remained symptom-free for 1 mo. Blue-light-blocking glasses also helped. Unfortunately, chronotherapy was not continued at home. Her rapid cycling resumed and 1 year later she dropped out of treatment; and (2) A 62-year-old woman with medication-resistant RCBD responded partially to morning bright light treatment combined with medication. Her depressive symptoms became less intense and the depressive episodes shorter. However, she was not able to carry out sleep deprivation treatment at home and her ultra-rapid cycling continued. She was hospitalized recently. Her depression responded to two cycles of triple chronotherapy and subsequent hypomanic symptoms responded to dark therapy and wearing blue-light-blocking glasses. She has achieved complete remission with

adjunctive chronotherapy after several years. Triple chronotherapy on an outpatient basis was planned for two more patients with treatment-resistant RCBD. It could not be implemented, but these patients responded to BLT, wake and dark therapy: (1) A 72-year-old man was able to undertake partial sleep deprivation for depression and dark therapy for hypomania at home with the help of his wife. He has achieved almost complete remission for the last 4 years with chronotherapy combined with medication, even though he had responded poorly to medications and ECT earlier; and (2) A 52-year-old woman with ultra-rapid RCBD could not undertake sleep deprivation at home. She has been undergoing morning bright light treatment for depression. Her response has been better since this treatment was added to her mood-stabilizer regimen. She has achieved almost complete remission after a long time. The treatment histories (Supplementary Material) of these patients illustrate the benefits and challenges of administering chronotherapy in RCBD[144]. Although wake therapy, BLT, triple chronotherapy, dark therapy, and blue-light-blocking glasses were successful, conducting these treatments at home was difficult because patients are unwilling to undertake sleep deprivation. Additionally, light boxes are expensive and few patients can afford them.

Adjunctive psychotherapy in RCBD

The existing literature on the treatment of BD indicates that the concomitant use of pharmacotherapy and psychotherapy significantly improves several patient outcomes[145-149]. The most effective forms of psychotherapy are psychoeducational treatments, CBT, and family-focused treatments. These are useful in decreasing symptom severity, reducing the duration of manic and depressive episodes, preventing recurrences, reducing residual depressive symptoms, and decreasing the number and duration of hospitalizations. Additionally, they improve medication adherence, illness management skills, coping abilities, and functional outcomes.

Despite the extensive evidence on the positive effects of adjunctive psychotherapy in BD, there are only a few reports of psychotherapy in RCBD. Table 3 shows these studies[51,58,150-153]. They provide some support for adjunctive psychoeducational treatments, CBT, family intervention, and supportive psychotherapy in RCBD. The outcomes obtained are similar to those shown by RCTs of adjunctive psychotherapy in BD.

The lack of studies on concomitant psychotherapies in RCBD is surprising because these treatments could yield better outcomes in RCBD. Moreover, this is contrary to the advice that psychoeducation, CBT, family interventions, and supportive psychotherapy should be used in RCBD because of the strong evidence base supporting the efficacy of adjunctive psychotherapy in BD[25,32,45,48,51].

Adjunctive psychotherapy in RCBD: patient example

One of our patients with treatment-resistant RCBD received adjunctive supportive therapy. A 42-year-old woman with ultra-rapid and ultradian cycling did not improve with medications and ECT. During the third period of hospitalization in 2015, she was started on regular sessions of structured psychotherapy. The strategies adopted included problem-solving to deal with day-to-day stresses and mood swings and supportive–expressive sessions to deal with more enduring problems such as interpersonal conflicts, and regrets about not working or marrying. She had her best period of mood stabilization for several months while she underwent psychotherapy. Unfortunately, she dropped out of the sessions and was following up irregularly till recently. Nevertheless, she remained free from any severe mood episodes with medications. She has had a recent relapse when medication doses were reduced to minimize side effects but improved with crisis intervention sessions. She has resumed supportive psychotherapy. Her treatment history (Supplementary Material) shows the usefulness of psychotherapy even in those who have not responded adequately to medications or ECT.

DISCUSSION

Treating RCBD remains a challenge for clinicians. Difficulties arise from its high prevalence, severity, poor outcomes, and high disability. The response to pharmacotherapy is often not adequate or complete. Therefore, nonpharmacological treatments are necessary for effectively managing RCBD[18,36,46-48]. However, research on adjunctive nonpharmacological treatments is still scarce[17,18,46,54]. This review shows that there has been limited progress in this area in the last 15 years[45]. A principal reason for the lack of data is the difficulty in conducting methodologically sound treatment trials in RCBD[18,44]. The treatment-resistant nature of RCBD creates further hurdles. Consequently, most RCTs of nonpharmacological treatments for BD usually exclude patients with RCBD.

Nevertheless, there are some promising developments. Not surprisingly, there have been more studies and reports since the 2007 review. Similar to the previous review, the current one also found that most of the evidence favours concomitant ECT as an acute and maintenance treatment in RCBD. Adjunctive acute ECT is effective for severe mood episodes in RCBD that are refractory to medication and have high risk of harm. Adjunctive maintenance ECT may prevent further rapid cycling, especially in those who respond favourably to acute ECT. There is an increasing interest in chronotherapy for BD, but the evidence concerning RCBD is still limited. However, unlike the earlier review, there appears to be preliminary evidence that wake therapy, BLT, dark therapy, and triple chronotherapy can provide better outcomes when combined with medication. Widespread use of these treatments has been hampered by a lack of funding for researchers and lack of awareness and expertise among clinicians[85,154]. Several other factors also hinder the use of chronotherapy, including the cost of equipment such as light boxes, the difficulty of conducting these treatments in outpatient settings or homes, and the problems in ensuring adherence to the treatment protocols[144,155-157]. Lastly, the scarcity of research on adjunctive psychotherapy in RCBD was particularly disappointing. Although psychotherapy appear to be commonly used in clinical settings, the lack of controlled evidence possibly reflects the difficulty in

Table 3 Studies of adjunctive psychotherapy in rapid-cycling bipolar disorder

Ref.	Type of study	Sample	Intervention	Results
Levy and Remick[51], 1986	Observational study	8 women with RCBD	Supportive psychotherapy with patients and family regarding treatment response and adherence	Complete remission in 5 patients and partial remission in 3 patients for 7–40 mo with combined psychotherapy and medications
Spurkland and Vandvik [150], 1989	Case report	13-yr-old girl with RCBD	Family therapy to reduce conflicts and improve adherence	Family therapy combined with medications led to lasting remission
Benjamin and Zohar[58], 1992	Case report	45-yr-old man with treatment-resistant RCBD	Supportive psychotherapy	Psychotherapy provided relief from the rapid-cycling pattern for 3 mo
Satterfield [151], 1999	Case report	33-yr-old man with medication-resistant RCBD	Pharmacotherapy and concomitant CBT	Significant reductions in the severity of manic, depressive, and anxiety symptoms with adjunctive CBT
Reilly-Harrington *et al*[152], 2007	Uncontrolled trial	10 patients with RCBD	CBT included psychoeducation, cognitive restructuring, and teaching illness-management skills	CBT over 5 mo led to significant improvements in depressive symptoms for 2 mo after the treatment in 6 patients who completed the trial
Lenz *et al* [153], 2016	Controlled trial	16 patients with RCBD; 14 wk of adjunctive psychotherapy and 12-mo follow-up	CPT *vs* BT. CPT included psychoeducation and CBT; BT consisted of reading and discussing a book on bipolar disorder	Significant effects of both treatments - reductions in illness severity, reductions in the number of all episodes with CPT and depressive episodes with BT, reductions in the number and duration of hospitalizations, reductions in disability, and improvement in medication adherence and illness concepts. CPT was better than BT

BT: Bibliotherapy; CBT: Cognitive behavioural therapy; CPT: Cognitive psychoeducational therapy; RCBD: Rapid-cycling bipolar disorder.

conducting psychotherapy trials for RCBD. Nevertheless, there is reason to believe that psychotherapy may be effective in RCBD because it can augment the response to medication, reduce acute and residual depression, improve functioning, promote recovery, and decrease family burden[45,48,51,158]. Studies show that childhood maltreatment, stressful life events, and disturbed family environments are more common in RCBD[2,9,25,48,50]. Adjunctive psychotherapy that addresses these factors and reduces psychosocial stress may be helpful in RCBD[45]. Medication nonadherence is a significant problem in BD. It is associated with adverse clinical and psychosocial outcomes among patients and their families. Although some studies show greater nonadherence in RCBD, the majority do not[159]. Nonadherence may be more common in those with more frequent episodes, higher disability, and in those with comorbid substance use disorders[10,40,160,161]. Rapid cycling with these features may contribute to nonadherence and inadequate adherence may worsen cycling[51]. Psychoeducational treatments help improve adherence and attitudes towards medication for BD [145,149]. Similarly, adjunctive psychosocial treatment can positively impact treatment adherence in RCBD by improving treatment attitudes, managing comorbid disorders, and minimizing disability[51,153]. Thus, despite the limited evidence many authors have recommended that adjunctive psychotherapy should form an essential part of the overall management of RCBD[26,32,45,49,158].

CONCLUSION

RCBD is a common phase in the course of BD characterized by greater severity, a predominance of depression, higher levels of disability, and poorer overall outcomes. It is resistant to treatment by conventional pharmacotherapy. The ineffectiveness of conventional pharmacological treatment for RCBD suggests that adjunctive nonpharmacological interventions could be useful but these have not been examined adequately.

According to this review, most of the evidence favoured concomitant ECT as an acute and maintenance treatment for medication-resistant RCBD. Although ECT is effective in refractory mania as a part of RCBD, a better response is obtained in depression with psychotic or catatonic symptoms. ECT is safe and the risk of inducing rapid cycling is low.

Among chronotherapeutic techniques, sleep deprivation or wake therapy has been the option most frequently investigated. Sleep deprivation is effective in relieving depressive symptoms but there is a high rate of relapse and the risk of inducing manic switches. Triple chronotherapy, which combines partial sleep deprivation, bright light treatment, and phase advance of the sleep cycle produces enduring effects and lowers the risk of manic switches. Although there are no studies of triple chronotherapy, examples of patients included in this review suggest that it can be successful in medication-resistant patients. Similarly, there are no studies of dark therapy or blue-light-blocking glasses, but these techniques have been successfully used to treat hypomania in individual patients. Case reports and studies also suggest that bright light treatment can be effective for patients with depression as a part of RCBD.

A few studies provide some support for adjunctive psychoeducational treatments, CBT, family intervention, and supportive therapy in medication-resistant RCBD. The overall quality of evidence for the usefulness of adjunctive nonpharmacological treatment in RCBD was poor and suffered from several methodological shortcomings.

It is apparent from this review that there are large gaps in the existing literature on the usefulness of adjunctive nonpharmacological treatments in RCBD. Therefore, examining the role of these treatments remains a priority for research. However, the current evidence regarding effective pharmacological and nonpharmacological treatment is inconclusive. Thus, clinicians may find treating RCBD a formidable task in the absence of specific guidelines. One option could be to select nonpharmacological treatments effective in BD[27,30,45,49]. Alternatively, treatment decisions can rely on the current evidence on nonpharmacological treatments in RCBD[18]. Clinicians can use this evidence to undertake the sequential or concurrent use of several pharmacological and nonpharmacological interventions[26,45]. Although this remains an exploratory exercise, such combinations are likely to succeed if individualized to meet the needs of patients with RCBD and their families. Table 4 includes principles derived from the existing recommendations that could guide clinicians in managing RCBD. As always, the key to successful treatment of RCBD requires patience, perseverance, and a strong collaborative relationship with patients and their families.

Table 4 Suggestions for the use of adjunctive nonpharmacological treatments in rapid-cycling bipolar disorder

	Suggestions
Goals of acute treatment[18,45]	The priority for acute treatment is to ensure that patients respond to treatment and no longer meet criteria for an acute mood episode
	A rapid response is necessary to provide relief for patients and their families and reduce the risks of self-harm, aggression, and physical complications
	The concurrent and early use of treatments such as ECT or wake therapy for depression, and dark therapy for mania may be considered if there is inadequate response to pharmacotherapy
	Treatments that are likely to be useful during long-term treatment should guide the use of treatments in the acute phases
Goals for long-term treatment[29,30,45,51,55]	Rather than focusing on acute treatment, the primary objective should be to prevent further episodes of rapid cycling
	The model for a chronic medical disorder with acute exacerbations should guide the long-term treatment plan for RCBD
	Adjunctive maintenance ECT, wake therapy, bright light treatment, dark therapy, and triple chronotherapy can be considered at this stage
	Education, support, and the involvement of the family is useful for all patients. Psychoeducational treatments, CBT, family treatment can be implemented if required
Improved functioning rather than complete remission should be the goal of long-term treatment[18,20,25,30]	Full remission and complete absence of recurrences is an unrealistic goal
	Clinicians should focus on an enduring response that consists of reduced frequency, intensity, and duration of mood episodes
	Clinicians should attempt to restore optimal functioning in the occupational, family, and social spheres
Basic tasks[2,4,54,55,162]	Careful diagnosis and comprehensive assessment of the patient including psychosocial factors
	Avoidance of precipitants such as stress, irregular sleep routines, and antidepressant medications when it worsens the course of RCBD
	Treatment of physical and psychiatric comorbidities especially hypothyroidism and substance use
Longitudinal approach and use of life charts [2,26,45,55,163]	Acute episodes should be viewed in the context of the long-term course of bipolar disorder/RCBD
	Life charts may be used to delineate the course of illness, possible precipitants, and treatment response. They might help patients and families understand the course of RCBD and the longitudinal approach to treatment
Use of treatments effective in bipolar disorder[27,30,45,49]	Options for adjunctive nonpharmacological treatment should be chosen based on the evidence for their efficacy in BD
Sequential trials of treatment for long durations[25-27,30,51]	Treatment of RCBD requires several trials of each treatment regimen lasting for about 3–4 mo before the acute-phase efficacy of the treatment regimen can be determined
	Frequent changes in treatment should be avoided since they might worsen rapid cycling
Combining pharmacological and nonpharmacological treatments[25,30,32,45,163]	One option is to add nonpharmacological treatments only in refractory patients in whom several medications have been tried and have failed
	An alternative option recommends the early use of adjunctive nonpharmacological patients even in those patients who are not medication resistant
Monitoring treatment response[17,18,25,35,	More intensive monitoring during acute phases which can be relaxed once the patient becomes more stable

51]	Mood charts can be used to assess response to treatment At least 12 mo of treatment is required to determine the efficacy of long-term treatment
Working with patients and families[4,32,45,51,127]	Education: explaining RCBD, its causes, and the treatment approach including lifestyle changes is necessary for ensuring the collaboration of patients and families. Psychoeducational treatments that reduce stress, improve attitudes to treatment, enhance treatment engagement, and reduce caregiver burden can be tried. CBT is another option Support: ongoing support for patients and families is essential. This can be provided by developing a strong collaborative relationship. Nonadherence can also be addressed by fostering a strong treatment alliance Patience: the protracted nature of the illness requires the clinician to accept that it will take a long time for the results to become apparent. Patience and perseverance on the part of patients and families has to be stressed repeatedly so that they learn to focus on long-term goals Sleep hygiene: regular sleep routines can be advised in all patients. Chronotherapeutic techniques can be tried when required and feasible

CBT: Cognitive behavioural therapy; ECT: Electroconvulsive therapy; RCBD: Rapid-cycling bipolar disorder.

FOOTNOTES

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ORIGINAL ARTICLE

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Dexmedetomidine mediates the mechanism of action of ferroptosis in mice with Alzheimer's disease by regulating the mTOR-TFR1 pathway

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Abstract

BACKGROUND

Alzheimer's disease (AD) is the most common neurodegenerative disorder, and there are currently no effective drugs to delay progression of the disease. Ferroptosis may play a vital part in AD, and is therefore receiving increasing attention by researchers.

AIM

To investigate the effects of dexmedetomidine (Dex) on ferroptosis in AD mouse hippocampus.

METHODS

Hippocampal neurons (HNs) HT22 were induced by amyloid β-protein (Aβ) and both *in vitro* and *in vivo* AD mouse models were prepared *via* injections. The cell-counting kit-8 assay and immunofluorescence technique were adopted to determine cell proliferation activity and intracellular Fe^{2+} levels, and the TBA method and microplate method were employed for malondialdehyde and glutathione measurements, respectively. Hippocampal tissue damage was determined using hematoxylin and eosin and Nissl staining. Mouse learning and memory ability in each group was assessed by the Morris water maze test, and the expression levels of mammalian target of rapamycin (mTOR) signal molecules and ferroptosis-related proteins transferrin receptor 1 (TFR1), SLC7A11 and glutathione peroxidase 4 were examined by western blotting.

RESULTS

Dex enhanced lipid peroxidation and iron influx in mouse HNs in both *in vitro* and *in vivo* experiments, while inhibition of the mTOR axis blocked this process. These findings demonstrate that Dex can inhibit ferroptosis-induced damage in mouse HNs by activating mTOR-TFR1 signaling to regulate ferroptosis-associated

proteins, thus alleviating cognitive dysfunction in AD mice.

CONCLUSION
Dex can activate the mTOR-TFR1 axis to inhibit ferroptosis in mouse HNs, thereby improving the learning and memory ability of mice.

Key Words: Dexmedetomidine; Ferroptosis; Alzheimer's disease; Mammalian target of rapamycin; Mice

Core Tip: Iron death of nerve cells caused by iron overload is an important factor in various neurodegenerative diseases, including Alzheimer's disease (AD). The classic mammalian target of rapamycin (mTOR) signaling pathway regulates the metabolism of iron ions by regulating transferrin receptor 1 (TFR1), thereby maintaining the intracellular iron balance. It has been shown that dexmedetomidine (Dex) inhibits the release of inflammatory factors and plays a neuroprotective role, thereby improving cognitive dysfunction in elderly rats. The Dex effectively improved hippocampal neuronal loss, cognitive dysfunction, learning and memory abilities in AD mice by regulating the mTOR-TFR1 signaling pathway to reduce iron death.

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INTRODUCTION

With the current escalation in global aging, neurodegenerative disorders (NDDs), including Alzheimer's disease (AD), Parkinson's disease, and Huntington's disease, have attracted growing attention from researchers and have become a research hotspot[1]. Ferroptosis is a non-apoptotic programmed cell death associated with cytotoxicity caused by iron-dependent lipid peroxide accumulation, and iron overload is the key to triggering the occurrence of cell ferroptosis[2]. It is reported that iron deposition in brain tissue increases significantly with age, ultimately affecting nerve cell function[3-5]. Immunohistochemical tests confirmed that neuronal ferroptosis caused by iron overload in the cerebellum, cortex and hippocampus was an important factor leading to NDDs. The mammalian target of rapamycin (mTOR) is a classical autophagy-dependent regulatory protein that affects cell death pathways such as autophagy, apoptosis, and ferroptosis [6]. The classic mTOR axis influences iron ion metabolism by modulating transferrin receptor 1 (TFR1), thus maintaining the intracellular iron balance[7]. In addition, the high intracellular Fe^{2+} level leads to the inhibition of mTOR expression, resulting in intracellular iron homeostasis imbalance and consequently oxidative stress (OS)-induced ferroptosis[8]. Dexmedetomidine (Dex) is a highly selective α2 adrenergic receptor agonist that not only exerts analgesic and sedative effects by inhibiting sympathetic nerve activity, but is also neuroprotective against various brain injuries[9,10]. However, its underlying mechanism is unknown. Several studies have found that, by regulating ferroptosis, Dex can play a protective role in liver injury, myocarditis, cerebral ischemia-reperfusion, and craniocerebral injury[11-13]. In addition, Dex was shown to significantly improve neurocognitive function and effectively inhibit the abnormally high level of OS in NDDs and brain trauma, thus reducing inflammation[14]. Yet, it remains to be confirmed whether and how Dex can be neuroprotective by regulating ferroptosis in AD, a NDD. The experimental results of this study show that Dex can inhibit iron overload by activating the mTOR-TFR1 axis, thus maintaining iron homeostasis, protecting hippocampal neurons (HNs) from ferroptosis, and playing a neuroprotective role in AD mice, which can provide insights into ferroptosis-induced neuronal death.

MATERIALS AND METHODS

Experimental animals

Forty adult male specific pathogen free C57BL/6 mice, aged 8-10 wk and weighing (23 ± 2) g, were raised under constant temperature (25 ± 1 °C), humidity (60% ± 5%), and an alternating light/dark (12/12 h) cycle. The experiments were carried out after 7 d of adaptive feeding with rat chow and water available *ad libitum*. All animal experiments were carried out after obtaining approval from the Experimental Animal Ethics Committee of Peking University International Hospital.

Experimental reagents

Mouse HT22 HNs and dedicated cell culture medium (Procell Life Science & Technology, Wuhan, China); Dex (Chia Tai

Tianqing Pharmaceutical Group, Nanjing, China); BCA analysis kit (Boster, China); cell-counting kit-8 (CCK-8; Dojindo, Japan); Perls stain (Thermo Fisher Scientific; United States); Nissl stain (Jiangsu KeyGEN Biotech, Nanjing, China); polyvinylidene fluoride (PVDF) membrane (Millipore, United States); malondialdehyde (MDA) Colorimetric Assay Kit (Abcam, United States); Mito-FerroOrange (Dojindo Molecular Technologies, Tokyo, Japan); 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) fluorescence probe (Solarbio, Beijing); Lipofectamine 2000 (Invitrogen, United States); siRNA mTOR (Shanghai Sangon Biotech, China); specific primary antibodies (Abs) and HRP labeled anti-p-mTOR, TFR1, SLC7A11 and glutathione peroxidase 4 (GPX4), as well as the internal reference GAPDH secondary Ab (Abcam, United States) were used in this study.

Experimental instruments

The Morris water maze (MWM) system (Noldus, Netherlands); inverted fluorescence biomicroscope (Zeiss, Germany); E0970 Microtome Cryostat (Beyotime Biotech, Beijing, China); enhanced chemiluminescence (ECL) detection system (Bio-Rad, Hercules, CA, United States); Multiskan FC microplate reader (Thermo Scientific, United States); western blot Electrophoresis Instrument and Trans-Blot instrument (Bio-Rad, United States) were used in this study.

Animal grouping and model building

Forty C57BL/6 mice were randomized to the sham, amyloid β-protein (Aβ), Dex, and Dex + rapamycin (RAPA) groups, with 10 mice in each group. After anesthesia by intraperitoneal injection of 10% chloral hydrate (dosage: 0.1 mL/10 g body weight) in all C57BL/6 mice, 5 μL of condensed Aβ (80 pmol/μL) was injected as a single bolus into mouse bilateral ventricles using a micro-sampler, and the needle was left in place for 2 min before bandaging. The sham group was injected with an equal amount of normal saline into the bilateral ventricles. The Dex group was intraperitoneally injected with Dex (dosage: 20 μg/kg) dissolved in 0.9% sterile saline, once a day for 4 consecutive weeks; on this basis, the Dex + RAPA group was additionally injected with 2 mg/kg of RAPA dissolved in 2% dimethylsulfoxide. The sham and Aβ groups were given the same amount of 0.9% sodium chloride solution, and the remaining treatment was the same as above.

MWM test

After the above treatment, the mice underwent the MWM test for 5 d. During the training phase (the first 4 d), the mice were trained once a day at a fixed time, and the time they took to find the platform within 120 s (*i.e.*, escape latency) and the swimming trajectory map were recorded. On the fifth day, the platform was removed for spatial exploration experiments, and the running trajectory, escape latency, number of platform crossings, and target quadrant residence time were recorded.

Animal tissues

The mice were anesthetized with chloral hydrate after the MWM test. The right auricle was then cut open and the left ventricle was perfused with 4% paraformaldehyde solution. After sacrifice on ice by cervical dislocation, the mouse hippocampus tissues on both sides were quickly removed, some of which was stored in liquid nitrogen for later use. The remaining portion was fixed in 4% paraformaldehyde, and after gradient dehydration with ethanol, it was embedded in paraffin and sliced into sections (4 μm). The pathological changes of HNs were observed under a light microscope after conventional hematoxylin-eosin (HE) staining.

Nissl staining

Part of the hippocampus tissue was frozen in liquid nitrogen to prepare frozen sections (5 μm), which were degreased with a gradient concentration of ethanol solution and then washed three times with ddH_2O for 30 s each time. Cresyl violet (Nissl) dye solution (0.1%) was added dropwise and left at 56 °C for 1 h. After dyeing, the slices were washed with ddH_2O for a further three times. Next, color separation was carried out for 2 min with acid alcohol differentiation solution (0.5%), followed by immersion in 100% ethanol for 30 s and xylene permeation for 1 min. After mounting with neutral gum, each slice was observed microscopically (400 ×) with five visual fields randomly selected, and the number of nerve cells was recorded (n = 5).

Prussian blue staining

Paraffin slices were routinely dewaxed and rinsed with distilled water for 1 min. Perls staining solution, which was homogeneously formulated by mixing reagent A1 with reagent A2 in equal amounts, was used immediately after preparation. The sections were washed again with distilled water after 30 min of Perls staining. They were then nucleated with the nuclear fast red stain kit (reagent B) for 10 min and rinsed with distilled water, followed by conventional dehydration, vitrification, neutral-gum mounting, and air drying. The Prussian blue deposition in hippocampal tissue was observed under a light microscope. Five visual fields in each slice were randomly photographed, and the percentage of Prussian blue staining (PBS) positive area in the whole area was measured by image analysis.

Cell cultivation and treatment

Mouse HT22 HNs were immersed in HT22 dedicated culture medium and cultivated in a 37 °C, 5% CO_2 and 95% humidified cell incubator, and the well-grown cells were selected for the following experiment. All neuron cell lines used were within 20 passages. Grouping: (1) Blank control group: HT22 cells was cultured with HT22-dedicated medium without any other treatment; (2) Aβ model group: HT22 cells were treated with Aβ at a final concentration of 20 μmol/L and cultured for 24 h; (3) Dex group: Following 2 h of treatment with Dex at a final concentration of 5 μmol/L, HT22 cells

were cultured with Aβ at a final concentration of 20 μmol/L for 24 h; and (4) Dex + mTOR siRNA (si-mTOR) group: After transfection with si-mTOR using Lipofectamine 2000, HT22 cells were treated with 5 μmol/L Dex for 2 h and then cultured with 20 μmol/L Aβ for 24 h.

CCK-8 assay

HT22 cells (1×10^5/mL) were seeded with 100 μL of cell suspension per well on a 96-well culture plate and cultured for 24 h. After different treatments, the CCK-8 reagent was added at 10 μL/well for 1 h at 37 °C, after which the absorbance value at 450 nm was measured by a microplate reader to assess cell viability.

Intracellular Fe^{2+} level detection

Intracellular Fe^{2+} levels were measured with Mito-FerroOrange. After different cell treatments, the supernatant was discarded. Following three rinses with HBSS, 2 mL of cells were added to every 2 μL of Mito-FerroOrange working solution and incubated at 37 °C for 30 min. The cells were observed by confocal fluorescence microscopy and the fluorescence intensity level was determined.

OS determination

Cell lipid peroxidation (LPO) was detected by BODIPY-C11 labeled fluorescent staining. 5 μM BODIPY-C11 was added to the cells and incubated in the dark for 20-30 min. After staining, the cells were collected by centrifugation and the LPO level was calculated by measuring the fluorescence intensity. In addition, HT22 cells were stained with 10 μM DCFH-DA fluorescent dye for 30 min, and were then collected for fluorescence intensity measurement, which reflected the reactive oxygen species (ROS) level. According to the manufacturer's instructions, the level of MDA, the final product of LPO, was determined using the MDA colorimetric assay kit. The absorbance of reactants was calculated and determined according to the standard curve to evaluate the MDA concentration.

Western blot

Following the standard protocol, HT22 cells in each group were lysed in RIPA buffer to extract the protein supernatant. In addition, the protein supernatants were isolated from the hippocampus following cryopreservation with liquid nitrogen and homogenized. The protein concentration was then quantitatively detected with a BCA assay kit. Following dilution and boiling, the protein samples were separated by 6%-10% polyacrylamide gel electrophoresis, after which semi-dry electroblotting was performed to transfer the protein bands to a PVDF membrane. The membrane was blocked in 5% defatted milk for 1 h, incubated with specific primary Abs at 4 °C overnight, washed with TBST twice, and incubated with HRP-labeled anti-p-mTOR, TFR1, SLC7A11 and GPX4 as well as the GAPDH specific secondary Ab (internal reference) for 1 h at ambient temperature. After dropwise addition of the ECL substrate to the protein bands, the grayscale values of the target protein bands were measured using the ECL detection system and the relative expression was calculated by the ratio of the grayscale values of the target protein to the reference protein.

Statistical analysis

Statistical processing and mapping of the data were performed using GraphPad Prism 7.0. Continuous variables that conformed to a normal distribution were described as the mean ± standard deviation (mean ± SD); statistical inter-group and multi-group differences, indicated by $P < 0.05$, were identified using the *t*-test and one-way variance analysis, respectively.

RESULTS

Dex blocks Aβ-induced cytotoxicity of mouse HNs by activating mTOR

In order to confirm whether Dex can alleviate the cytotoxicity of mouse HNs, we first measured the impact of Dex on the viability of Aβ-treated mouse HNs. As shown by the CCK-8 assay (Figure 1), Aβ-treated HNs showed notably weakened cell viability compared with HNs from blank control mice ($P < 0.05$), while Dex treatment significantly restored the viability of Aβ-treated HNs ($P < 0.05$); in addition, the viability of Dex + si-mTOR treated cells was significantly lower than that of Dex-treated cells ($P < 0.05$). These findings suggest that Dex can alleviate the cytotoxicity of Aβ-treated mouse HNs, while inhibiting mTOR can block the effect of Dex treatment on cytotoxicity.

Dex inhibits the increase of Fe^{2+} level in Aβ-treated mouse HNs by activating mTOR

To further examine whether ferroptosis was responsible for Aβ-induced inhibition of cell proliferation, we first measured the impact of Dex on Fe^{2+} levels in Aβ-treated mouse HNs. As shown in Figure 2, Aβ-treated mouse HNs showed markedly elevated Fe^{2+} levels ($P < 0.05$), which were significantly reduced by Dex treatment ($P < 0.05$); moreover, Dex and si-mTOR co-treatment led to statistically higher Fe^{2+} levels in Aβ-treated HNs compared with Dex treatment alone ($P < 0.05$). These results show that Dex can inhibit the Aβ-induced increase of Fe^{2+} level in mouse HNs, and this inhibition is achieved by activating mTOR.

Dex reduces Aβ-induced OS in mouse HNs by activating mTOR

The increase of intracellular OS level in mouse HNs is also an important feature of ferroptosis. Significantly elevated ROS, LPO and MDA levels were observed in Aβ-treated mouse HNs ($P < 0.05$), which were reduced after Dex treatment ($P <$

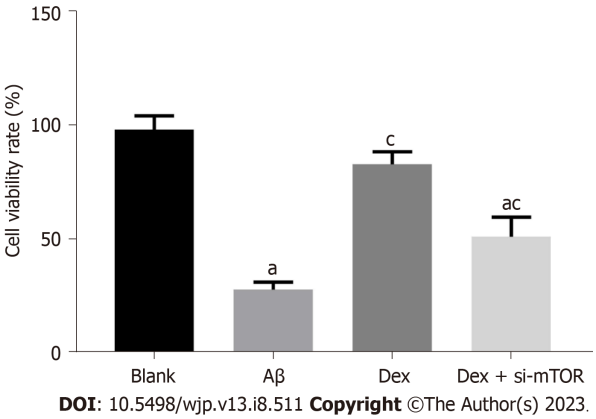

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Figure 1 Comparison of the activity levels of hippocampal neurons in mice in the different treatment groups. $^{a}P < 0.05$, compared with the blank group; $^{c}P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; si-mTOR: Mammalian target of rapamycin siRNA.

0.05); in addition, Dex and si-mTOR co-treated cells showed higher ROS, LPO and MDA levels than those treated with Dex alone ($P < 0.05$), as shown in Figure 3. These results suggest that Dex treatment can alleviate the increase in intracellular OS level induced by Aβ in mouse HNs, and inhibiting mTOR can block this process.

Dex blocks Aβ-induced ferroptosis in mouse HNs through regulation of the mTOR-TFR1 axis

In order to confirm whether the antioxidant protection and iron metabolism effects of Dex are related to ferroptosis in mouse HNs, we performed western blot to determine the expression levels of the mTOR signal molecular protein p-mTOR and ferroptosis-associated marker proteins TFR1, SLC7A11, and GPX4 in Aβ-treated mouse HNs. The results showed a marked reduction in p-mTOR, SLC7A11, and GPX4 protein expression in mouse HNs induced by Aβ, and an obvious increase in TFR1 protein expression ($P < 0.05$). Compared with the Aβ group, Dex-treated cells showed enhanced p-mTOR, SLC7A11 and GPX4 levels, and decreased TFR1 ($P < 0.05$). Simultaneous treatment with Dex and si-mTOR further reduced p-mTOR, SLC7A11 and GPX4 protein levels, and promoted TFR1 protein expression, and these changes were statistically significant ($P < 0.05$), as shown in Figure 4. Therefore, Dex can significantly activate mTOR signaling and reduce Aβ-induced ferroptosis in mouse HNs by modulating the mTOR-TFR1 axis.

Dex alleviates hippocampal tissue damage in AD mice by activating mTOR

According to HE staining results, the HNs in Sham mice were evenly distributed, with abundant cytoplasm, clear nuclei, and normal and intact cell morphology and structure; in the Aβ group, the HNs were sparsely arranged and disordered, with less cytoplasm, unclear cell morphology and atrophy; the HNs in the Dex group showed less neuronal atrophy, with uniform cell distribution, regular arrangement, and deep cytoplasmic staining; while HNs in the Dex + RAPA (mTOR inhibitor) group showed more atrophy, more irregular arrangement and less clear cell morphology than the Dex group. Nissl staining results demonstrated that Nissl bodies in the hippocampus of the sham group were closely arranged and in large numbers; a notably reduced number of Nissl bodies was observed in the hippocampus of the Aβ model group; following Dex treatment, the number of Nissl bodies in the hippocampus of the Aβ model mice increased significantly; while the Nissl body count in the hippocampus of the Dex + RAPA group decreased markedly compared with the Dex group (Figure 5). These findings indicate that Dex can mitigate Aβ-induced hippocampal tissue damage and increase the number of HNs in AD mice, and this process is realized through activation of mTOR signaling.

Dex mitigates OS and Fe^{2+} levels in AD mouse hippocampus by activating mTOR

To confirm whether the antioxidant protection of Dex is related to its regulation of iron metabolism, we further evaluated the influence of Dex treatment on OS and Fe^{2+} level in the mouse hippocampus. MDA in the hippocampus of AD model mice induced by Aβ was significantly increased compared with Sham mice, while glutathione (GSH) was markedly reduced ($P < 0.05$). The Dex group showed reduced MDA and elevated GSH compared with the Aβ group ($P < 0.05$); moreover, co-treatment with Dex and RAPA in AD mice showed enhanced MDA and decreased GSH in the hippocampus compared with Dex-treated AD mice ($P < 0.05$). In addition, based on PBS results, the level of Fe^{2+} in hippocampal tissue of Aβ-treated AD model mice was significantly increased ($P < 0.05$), and was markedly reduced after Dex treatment ($P < 0.05$); moreover, the Dex + RAPA group showed higher Fe^{2+} in hippocampal tissue than that in the Dex group ($P < 0.05$) (Figure 6). Thus, Dex can markedly alleviate iron deposition and OS in Aβ-treated AD mouse hippocampus by activating mTOR.

Dex reduces cognitive dysfunction in AD mice by activating mTOR

The MWM test was used to evaluate the learning and memory ability of mice in each group. AD mice in the Aβ group showed markedly prolonged escape latency, and a statistically significant reduced number of platform crossings and target quadrant residence time ($P < 0.05$). The escape latency, number of platform crossings and target quadrant residence time of AD mice in the Dex group and Dex + RAPA group were significantly improved compared with the Aβ group ($P < 0.05$), with improvement in cognitive dysfunction in the Dex group as compared with the Dex + RAPA group ($P < 0.05$),

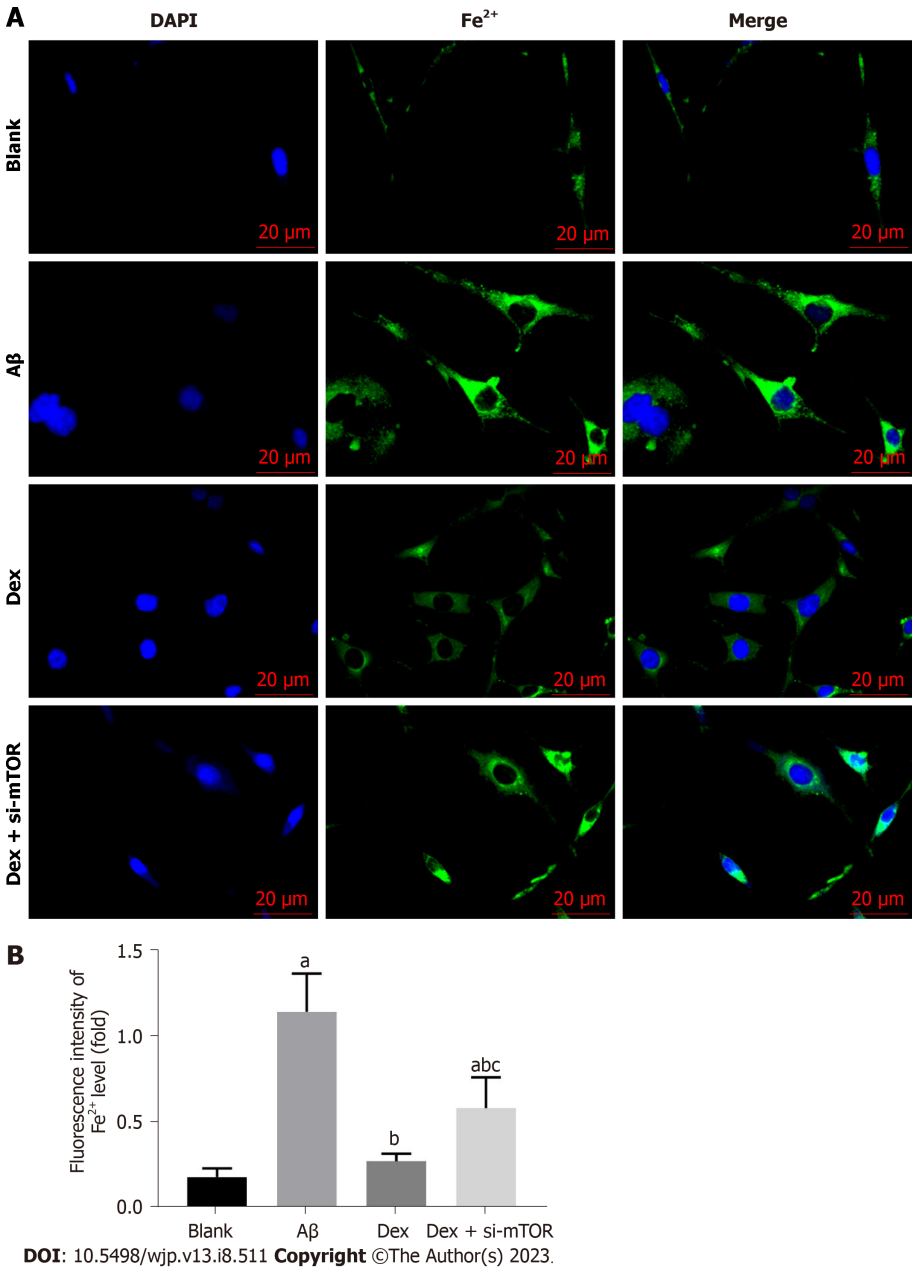

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Figure 2 Comparison of the level of Fe^{2+} in mouse hippocampal neurons in the different treatment groups. A: Green fluorescence represents intracellular iron levels, and quenching of calcein fluorescence reflects iron uptake by chondrocytes. Scale bar: 20 μm; B: Fluorescence intensity. $^{a}P < 0.05$, compared with the blank group; $^{b}P < 0.05$, compared with the amyloid β group; $^{c}P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; si-mTOR: Mammalian target of rapamycin siRNA; DAPI: 4',6-diamidino-2-phenylindole.

as shown in Table 1. These results suggest that Dex treatment improves the learning and memory ability of Aβ-treated AD mice, while RAPA exerts negative effects on this improvement.

Dex reduces ferroptosis in AD mice by modulating mTOR-TFR1

From the western blot analysis (Figure 7), it was found that the Aβ group had markedly reduced mTOR, SLC7A11 and GPX4 protein levels and elevated TFR1 protein expression in the hippocampus compared with the sham group ($P < 0.05$); Dex treatment enhanced mTOR, SLC7A11 and GPX4 protein expression in AD mice, and decreased TFR1 protein expression ($P < 0.05$); furthermore, the injection of RAPA effectively blocked the regulation of Dex on the expression of mTOR signaling molecules and ferroptosis markers TFR1, SLC7A11 and GPX4 in AD mouse hippocampus ($P < 0.05$). Therefore, Dex can mitigate ferroptosis in AD mouse hippocampus by activating the mTOR-TFR1 axis.

DISCUSSION

AD is the most common progressive NDD, and is mainly caused by synaptic loss of neurons in the cerebral cortex and

Table 1 Comparison of escape latency, number of platform crossings and target quadrant residence time in the different treatment groups

Groups	Sham (*n* = 10)	Aβ (*n* = 10)	Dex (*n* = 10)	Dex + rapamycin (*n* = 10)
Escape latency (s)	5.38 ± 0.53	42.20 ± 3.89[a]	13.81 ± 1.64[a,b]	22.75 ± 3.06[a,b,c]
Number of platform crossings (times)	7.26 ± 0.82	1.38 ± 0.35[a]	5.90 ± 0.61[a,b]	3.24 ± 0.43[a,b,c]
Target quadrant residence time (s)	38.46 ± 5.27	7.92 ± 1.69[a]	30.40 ± 4.26[a,b]	22.52 ± 2.78[a,b,c]

[a]$P < 0.05$, compared with the sham group.
[b]$P < 0.05$, compared with the amyloid β group.
[c]$P < 0.05$, compared with the dexmedetomidine group.
β: Amyloid β; Dex: Dexmedetomidine.

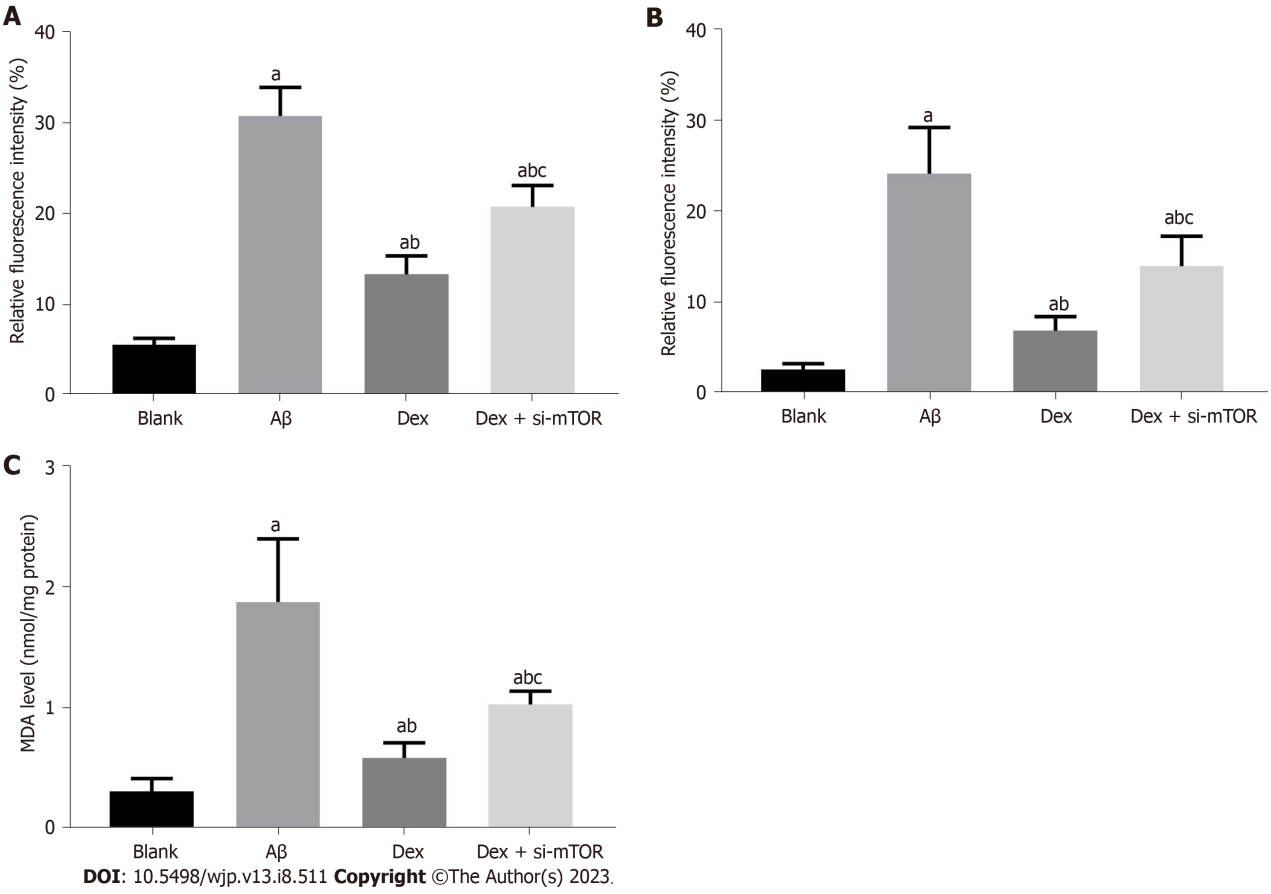

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Figure 3 Comparison of oxidative stress index levels in mouse hippocampal neurons in the different treatment groups. A and B: Hippocampal neurons were stained with DCFH-DA or C11 BODIPY fluorescent probe, reactive oxygen species (A) and lipid peroxidation levels (B) were calculated by measuring fluorescence intensity; C: Absorbance of the oxidation reaction was measured to evaluate the cellular malondialdehyde level using kits. [a]$P < 0.05$, compared with the blank group; [b]$P < 0.05$, compared with the amyloid β group; [c]$P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; si-mTOR: Mammalian target of rapamycin siRNA; MDA: Malondialdehyde.

hippocampus, and the death of brain neurons[15]. In recent years, ferroptosis has been found[16-18] to be the underlying mechanism of neuron loss in many NDDs, and the "ferroptosis hypothesis" has been proposed for AD. GPX4 mRNA and protein levels are reported to be aberrantly down-regulated in the brains of patients and mice with AD[19,20]. GPX4 relies on reduced GSH to catalyze LPO reduction, which is considered the key regulator of ferroptosis, while the inhibition of GPX4 can lead to LPO accumulation, a hallmark feature of ferroptosis that is considered an early event in the pathological process of AD[21]. During the process of iron imbalance, free Fe^{2+} released by ferritin degradation reacts with lipids through the Fenton reaction, and eventually forms lipid peroxy radicals and hydroperoxides, leading to LPO accumulation, the prime reason for ferroptosis[22]. The present study demonstrated that there were significant iron deposits and increased ROS and lipid oxidation levels in Aβ-treated mouse HNs and AD mouse hippocampus tissues, and Aβ treatment promoted the expression of iron transfer-related protein TFR1 and decreased the expression levels of ferroptosis regulation associated proteins GPX4 and SLC7A11. Furthermore, *in vitro* and *in vitro* studies demonstrated the

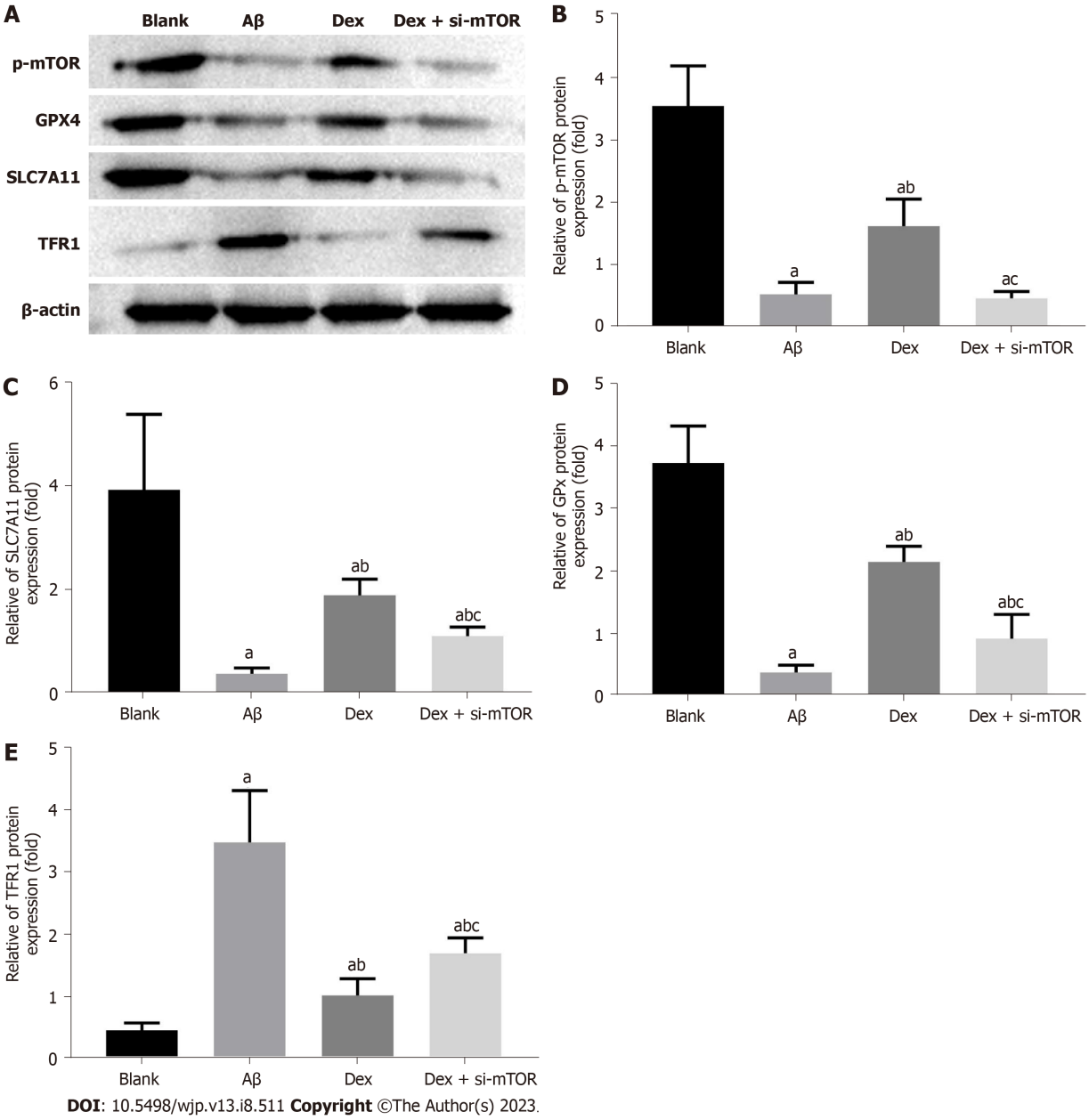

Figure 4 Comparison of iron death-related protein levels in hippocampal neurons of mice in the different treatment groups. A: Expression levels of p-mammalian target of rapamycin, SLC7A11, glutathione peroxidase 4, and transferrin receptor 1 were detected by western blot; B-E: The relevant data. [a]*P* < 0.05, compared with the blank group; [b]*P* < 0.05, compared with the amyloid β group; [c]*P* < 0.05, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; si-mTOR: Mammalian target of rapamycin siRNA; GPX4: Glutathione peroxidase 4; TFR1: Transferrin receptor 1.

occurrence of ferroptosis during AD. Thus, the above research suggests the important role of ferroptosis in AD.

Moreover, in the *in vivo* and *in vitro* experiments, it was found that Dex effectively reduced ferroptosis in HNs of AD mice. Previous studies have confirmed the neuroprotective effects of Dex, as it can inhibit the neuroinflammatory reaction and reduce OS, and has an anti-inflammatory and antioxidant role[23]. It has also been shown to prevent early cognitive dysfunction in senile mice after surgery[24]. Sun *et al*[25] also reported that Dex reduced Aβ1-induced HN apoptosis and OS responses in mice by modulation of the miR-129/YAP1/JAG1 axis, thus alleviating cognitive impairment and improving cognitive function in AD mice. In the present study, the number of Nissl bodies in the hippocampus of Aβ-treated AD mice decreased significantly compared with sham mice in the presence of neuronal atrophy, while intraperitoneal injection of Dex led to a marked elevation in Nissl body number in AD mouse hippocampus and an obvious reduction in neuronal atrophy. Moreover, the MWM test of mouse learning and memory ability in each group showed that the escape latency of AD mice in the Dex group was significantly shortened compared with the Aβ group, with a statistically significant higher number of platform crossings and target quadrant residence time, suggesting significantly reduced cognitive dysfunction in AD mice after Dex treatment. Considering the aforementioned inhibitory effect of Dex on ferroptosis of HNs in mice, it can be concluded that Dex can extend the survival of neurons by inhibiting HN ferroptosis, thus improving cognitive function in AD mice.

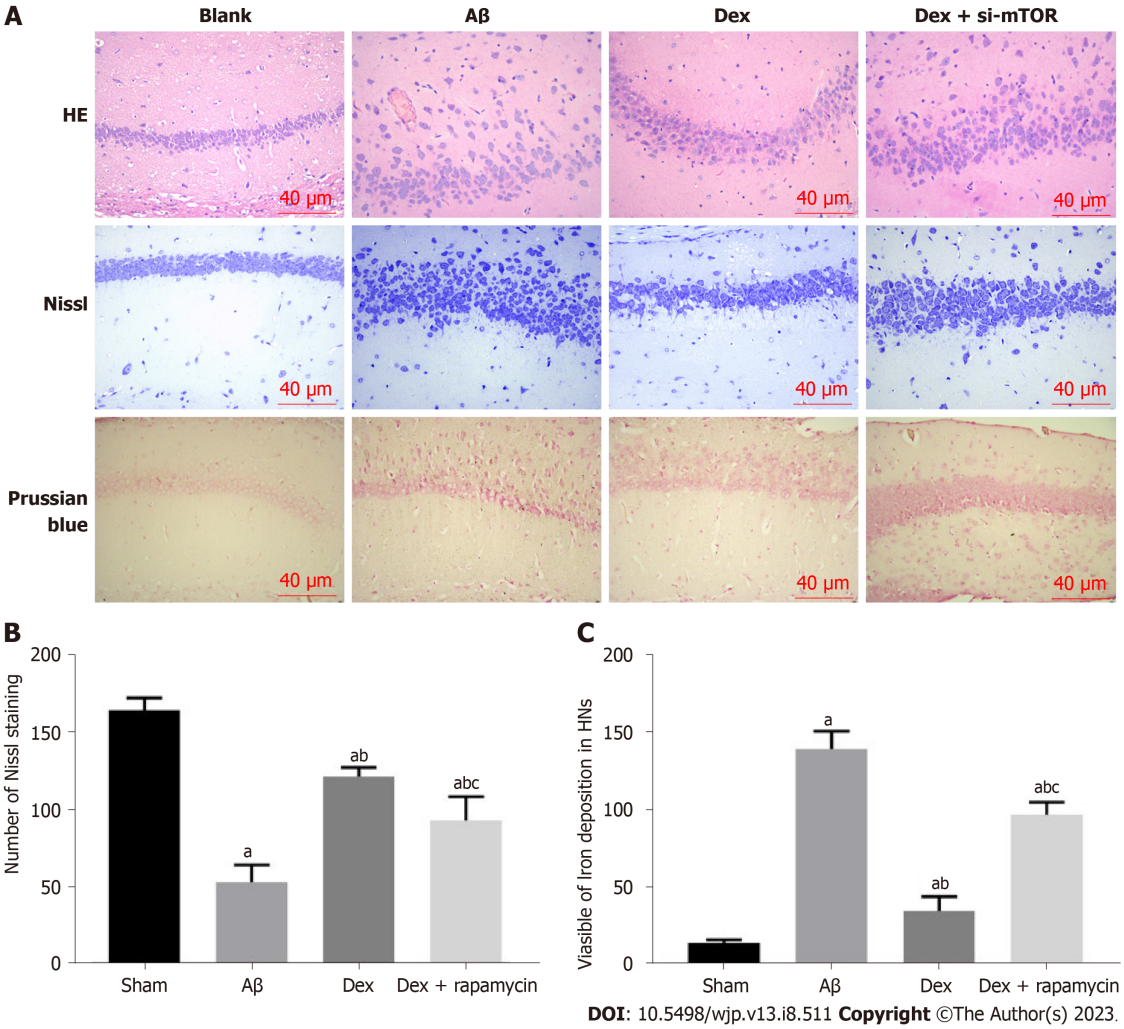

Figure 5 Comparison of pathological changes, nerve cell injury and iron deposition in mouse brain tissue in the different treatment groups. A: Hematoxylin and eosin, Nissl, and Prussian blue staining for pathological changes, neuronal damage, and iron deposition in the brain tissue of mice in each group. Scale bar, 40 μm; B: Representative photomicrographs of Nissl staining of surviving neurons in the hippocampal region, and statistical analysis of Nissl bodies in each group; C: Representative photomicrographs of Prussian blue staining of surviving neurons in the hippocampal region, and statistical analysis of iron deposition in each group. $^{a}P < 0.05$, compared with the sham group; $^{b}P < 0.05$, compared with the amyloid β group; $^{c}P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; si-mTOR: Mammalian target of rapamycin siRNA; HE: Hematoxylin and eosin; HNs: Hippocampal neurons.

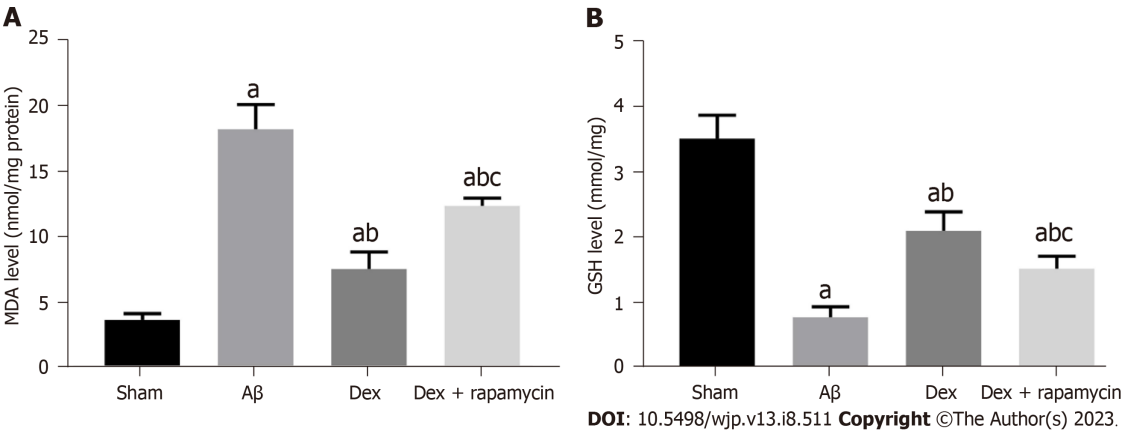

Figure 6 Comparison of oxidative stress index levels in mouse brain tissue in the different treatment groups. A: Absorbance of the oxidation reaction was measured to evaluate the cellular malondialdehyde level using kits; B: The activity levels of glutathione enzyme activity was measured using kits according to a colorimetric method. $^{a}P < 0.05$, compared with the sham group; $^{b}P < 0.05$, compared with the amyloid β group; $^{c}P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; MDA: Malondialdehyde; GSH: Glutathione.

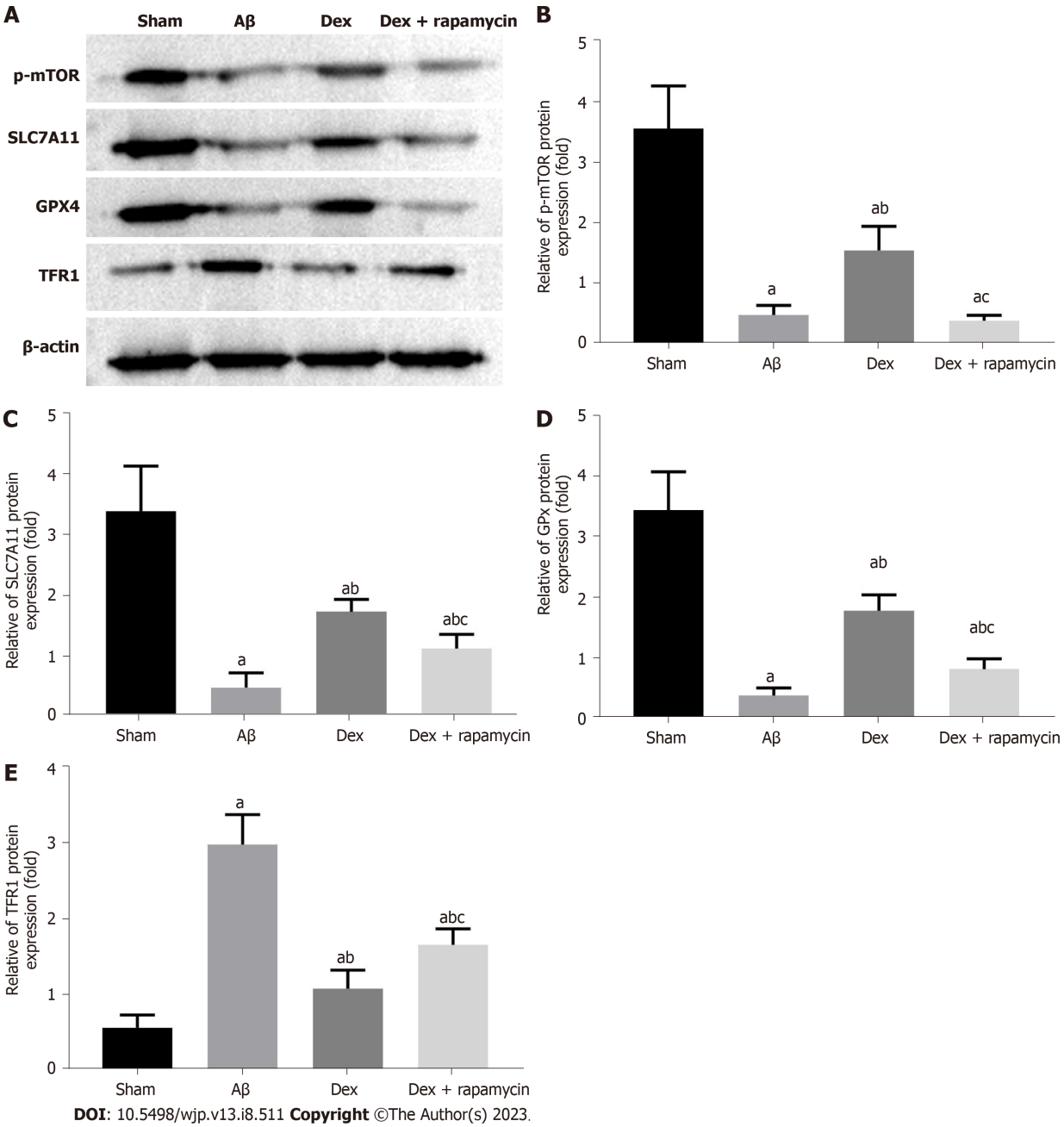

Figure 7 Comparison of iron death-related protein levels in mouse brain tissue in the different treatment groups. A: Expression levels of p-mammalian target of rapamycin, SLC7A11, glutathione peroxidase 4, and transferrin receptor 1 in mouse brain tissue were detected by western blot; B-E: The relevant data. $^{a}P < 0.05$, compared with the sham group; $^{b}P < 0.05$, compared with the amyloid β group; $^{c}P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; mTOR: Mammalian target of rapamycin; GPX4: Glutathione peroxidase 4; TFR1: Transferrin receptor 1.

The mTOR axis has been reported to play a regulatory role in cell death and apoptosis in various diseases such as aging, NDDs, and brain injury[26]. Increasing attention has recently been paid to the mechanism of mTOR mediated ferroptosis. It has long been reported that mTOR plays a regulatory role in upstream targets of iron metabolism, and that the mTOR-TFR1 axis is essential in balancing iron homeostasis by regulating TFR1 expression[27]. Our experimental results revealed that inhibition of the mTOR pathway significantly promoted Fe^{2+}, OS and TFR1 levels in mouse HNs, and lowered GPX4 and SLC7A11 expression, indicating that the ability of Dex to protect HNs from Aβ-induced ferroptosis and mitigate cognitive dysfunction in AD mice is weakened following inhibition of mTOR expression. It is suggested that Dex can reduce ferroptosis of HNs and ease cognitive dysfunction in AD mice, possibly by activating the mTOR axis.

CONCLUSION

Both *in vitro* and *in vivo* experiments in this study confirmed that Dex can inhibit Aβ-induced ferroptosis of mouse HNs, and effectively reduce HN loss and cognitive dysfunction in AD mice. Furthermore, Dex improved learning and memory

in AD mice by modulating the mTOR-TFR1 axis to reduce ferroptosis.

ARTICLE HIGHLIGHTS

Research background

The main pathological feature of Alzheimer's disease (AD) is the formation of amyloid β-protein (Aβ) plaques in the brain, leading to loss of neuronal synapses, ultimately affecting the patient's learning and memory abilities. Research has shown that iron death caused by iron overload in nerve cells is an important factor leading to neurodegenerative diseases, and plays a crucial role in the progression of AD. Recently, reports have demonstrated the high selectivity of dexmedetomidine (Dex), an α adrenergic receptor agonist, that can exert neuroprotective effects by inhibiting the release of inflammatory factors, thereby improving cognitive dysfunction in elderly rats.

Research motivation

Currently, there are still no effective drugs to delay the progression of AD, and iron death which may play a crucial role in the progression of this disease is attracting increasing attention from researchers.

Research objectives

To investigate the effect of Dex on iron death in the hippocampus of AD mice by both *in vitro* and *in vivo* research.

Research methods

Construction and utilization of an AD model using Aβ. The mouse hippocampal neuronal cell line HT22 was induced, and the levels of cell proliferation activity and intracellular Fe^{2+} were measured by the cell-counting kit-8 assay and immunofluorescence. The contents of malondialdehyde and glutathione were measured by the TBA method and microplate method, respectively. In the AD mouse model Aβ was injected, and the pathological damage in the mouse hippocampus was detected by hematoxylin and eosin staining and Nissl staining. The Morris water maze was used to evaluate the learning and memory abilities of mice in each group, and protein immunoblotting was used to evaluate the expression levels of p-mammalian target of rapamycin (p-mTOR) and iron death-related proteins transferrin receptor 1 (TFR1), SLC7A11, and glutathione peroxidase 4.

Research results

Dex significantly improved lipid peroxidation and iron influx in mouse hippocampal neurons (HNs) both *in vivo* and *in vitro*, and inhibition of the mTOR signaling pathway blocked this process, demonstrating that Dex can inhibit the damage caused by iron death in mouse HNs by activating mTOR-TFR1 signaling regulation, thereby improving cognitive dysfunction in AD mice.

Research conclusions

Dex can significantly activate the mTOR-TFR1 signaling pathway and inhibit iron death in mouse HNs, thereby improving the learning and memory abilities of mice.

Research perspectives

From *in vitro* and *in vivo* molecular experimental research, it is possible to analyze the effect of Dex on iron death in AD related nerve cells.

FOOTNOTES

Author contributions: Qiao L and Yuan HX conceived the study design and the content concept; Li G and Yuan HX performed data collection, extraction and analysis, interpreted and reviewed the data and drafts; Qiao L, Li G, and Yuan HX reviewed the final draft. Li G and Yuan HX are co-corresponding authors with equal contribution to the article.

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ORIGINAL ARTICLE

Basic Study

Pilot study of genome-wide DNA methylation and gene expression for treatment response to escitalopram in panic disorder

Zhi-Li Zou, Yuan Zhang, Yu-Lan Huang, Jin-Yu Wang, Bo Zhou, Hua-Fu Chen

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Abstract

BACKGROUND

Antidepressants, particularly selective serotonin reuptake inhibitors, are currently considered the first-line treatment for panic disorder (PD). However, little is known about the relationship between the biomarkers that may predict better treatment.

AIM

To compare genome-wide methylation and gene expression patterns between responsive and non-responsive patients with PD after 4 wk of escitalopram treatment.

METHODS

Thirty patients with PD were enrolled in this study (responders = 13; non-responders = 17). All patients were assessed using the PD Severity Scale-Chinese version before and after treatment. The Illumina Infinium MethylationEPIC (850k) BeadChip for genome-wide methylation screening and mRNA sequencing was used in all patients with PD.

RESULTS

A total of 701 differentially methylated positions (DMPs) were found between responders and non-responders ($|\Delta\beta| \geq 0.06$, $q < 0.05$), and the hyper- and hypomethylated CpG sites were 511 (72.9%) and 190 (27.1%), respectively. Relative to non-responders, there were 59 differential transcripts, of which 20 were downregulated and 39 were upregulated ($q < 0.05$). However, no differen-

tially expressed genes were identified by mRNA sequencing after correcting for multiple testing (|log2(FC)| > 1, q > 0.05).

CONCLUSION

This preliminary study showed that DMPs might be associated with the treatment response to escitalopram in PD; however, these DMPs need to be verified in large samples.

Key Words: Panic disorder; Methylation; Expression profiling; Escitalopram

Core Tip: No genome-wide methylation studies or mRNA sequencing have been conducted to identify early response biomarkers in patients with panic disorder (PD). This study aimed to compare genome-wide methylation and gene expression patterns between responsive and non-responsive patients with PD after 4 wk of escitalopram treatment. A total of 701 differentially methylated positions (DMPs) were found between responders and non-responders, and the hyper- and hypomethylated CpG sites were 511 (72.9%) and 190 (27.1%), respectively. This preliminary study showed that DMPs might be associated with the treatment response to escitalopram in PD.

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INTRODUCTION

Panic disorder (PD) is a common anxiety disorder characterized by recurrent and unexpected panic attacks. The estimated 12-month and lifetime prevalences of PD are 2.4% and 3.8%, respectively[1,2]. A cross-national epidemiological study reported that the lifetime prevalence of panic attacks was 13.2%[3]. Patients with PD experience symptoms such as tachycardia, chest pain, breathlessness, and dizziness. Consequently, they most frequently seek care in medical settings, such as emergency departments, and their condition is often undiagnosed[4]. PD causes substantial suffering and increases economic costs for both patients and society[5]. Hence, the availability of effective treatment may not only benefit individual patients but also provide economic returns to society.

Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are currently considered first-line treatments for PD. A meta-analysis suggested that SSRIs result in high remission rates with a minimal risk of adverse events in the treatment of PD[6,7]. However, not all patients benefit from the antidepressant therapy. For example, in a 12-week clinical trial of sertraline, citalopram, escitalopram, and paroxetine, 11.1%–18% of patients with PD did not respond to treatment[8,9]. Thus, predictive biomarkers of antidepressant response could greatly benefit clinical practice by decreasing the duration of drug efficacy evaluations.

Previous studies have found that common genetic variants could explain 42% of the individual differences in antidepressant response[10]. In addition, gene polymorphism studies focusing on *5-HTT*, *5-HTR1A*, *5-HTR2A*, *COMT*, *BDNF*, and *P450* (*CYP*) have been conducted in several large-scale studies on antidepressant drug responses in PD[11-14]. However, no consistent findings have been obtained from these studies. For example, with regard to treatment response to SSRIs in patients with PD, Zou *et al*[13] found that *5-HTTLPR* polymorphism, rather than *5-HTR1A*, may be an early predictor of response to sertraline in 2020, whereas Yevtushenko *et al*[11] indicated the importance of a *5-HT1A* receptor gene polymorphism in 2010. Therefore, genetic variation in a single gene cannot fully explain individual differences in the response to treatment.

Emerging evidence from human and animal studies suggests a key role of epigenetic markers, including DNA methylation and histone modifications, in the prediction of antidepressant response[15]. Methylation of some candidate genes, such as *SLC6A4*, *BDNF*, and *IL11*, has shown promising results as a biomarker for predicting antidepressant responses in major depressive disorder (MDD). However, the research methods and results have been heterogeneous [16]. Genome-wide methylation analysis can accurately determine the location of DNA methylation in the genome and screen for effect-related differentially methylated genes. Currently, 850k methylation BeadChip is a new generation of DNA methylation chips developed based on the original 450k methylation chip[17]. The newly developed Human Methylation 850 BeadChip covers over 850k CpG methylation sites and is the most useful tool for analyzing the DNA methylation profile of the human genome. In addition, DNA methylation is a key epigenetic mechanism involved in the developmental regulation of gene expression[18]. Nevertheless, no genome-wide methylation studies or mRNA sequencing have been conducted to identify early response biomarkers in patients with PD.

Hence, a pilot study of genome-wide DNA methylation and gene expression analysis was conducted in patients with PD using the Illumina 850k BeadChip and mRNA sequencing to identify possible predictors of treatment response to escitalopram.

MATERIALS AND METHODS

Study sample

All patients with PD were recruited from the inpatient and outpatient departments of Sichuan Provincial People's Hospital between March 2019 and December 2020. All patients satisfied the following inclusion criteria: (1) Primary diagnosis of PD in line with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) performed by a professional psychiatrist through a standardized structured clinical interview for DSM-IV Axis I disorders[19], with none of the patients having any other psychiatric disorders; (2) All PD patients were medication-naïve and had no history of any antidepressant or other psychotropic medication intake; (3) All subjects were without suicide ideations and attempts; (4) Subjects had no family history of psychiatric disorders in a first-degree relative; (5) All patients were Han Chinese aged 18 to 60 years; (6) All subjects were free of acute or chronic somatic disorders, head trauma, or neurological illnesses, and all subjects were free of alcohol consumption within 2 wk before their examination. Women were non-pregnant and non-nursing; and (7) All patients received escitalopram (10–20 mg qd) for 4 wk. The study was approved by the Sichuan Provincial People's Hospital ethics committee [reference number: (2021) Ethics Review (313)]. All individuals provided written informed consent prior to the initiation of study procedures.

Clinical assessment

Patients were assessed at baseline and after 4 wk of treatment using the PD Severity Scale (PDSS). The PDSS comprises seven items, and participants are instructed to rate each item from 0 (none) to 4 (extremely severe) based on the severity of each symptom[20]. The PDSS-Chinese version has good internal consistency (Cronbach's alpha) with an overall score of 0.83[21]. Treatment response for PD was defined as a reduction in the pretreatment PDSS score of at least 40% at 4 wk [22]. The PD samples were divided into responder and non-responder groups.

DNA and RNA extraction

A 4-mL ethylenediaminetetraacetic acid-anticoagulated peripheral blood sample was collected from all subjects in a fasting state *via* venipuncture between 7:00 a.m. and 8:30 a.m. DNA and RNA were extracted from whole blood samples from PD patients at baseline using DNeasy Blood and miRNeasy Mini kits (Qiagen, Hilden, Germany), respectively, according to the manufacturer's protocol.

Genome-wide DNA methylation analysis

DNA was subjected to sodium bisulfite conversion using the EZ DNA Methylation Kit (Zymo Research, Irvine, CA, United States). The Illumina Infinium Human Methylation 850K BeadChip (Illumina, San Diego, CA, United States) was used to assess genome-wide DNA methylation, with a genome-wide coverage of over 850k CpG methylation sites per sample according to the manufacturer's instructions. DNA quality control, bisulfite conversion, genome-wide methylation analysis, and initial methylation signal detection quality control were performed by Sinotech Genomics Co., Ltd. (Shanghai, China).

The raw intensity data were imported into R (v4.0.0; R Foundation for Statistical Computing, Vienna, Austria) and analyzed using the ChIP (ChAMP) package (v2.18.2) for data preprocessing, normalization, and comparison. β-values (ranging from 0 to 1) were used to determine the DNA methylation levels at each CpG site. Probes were filtered, including probes with a detection p-value of < 0.01, probes with less than three beads in at least 5% of the samples, non-CpG probes, and multi-hit probes. Beta-Mixture Quantile was used to normalize β-value matrices to adjust for type I and II probe biases[23]. In addition, we used singular value decomposition analysis to analyze the batch effect caused by the BeadChip Slide and Array and applied Combat to correct this batch effect[24]. Finally, all CpG sites were annotated using EPICanno software. ilm10b5. hg19.

Gene expression analysis

An Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, United States) was used to assess RNA quality. A Qubit® 3.0 Fluorometer (Thermo Fisher Scientific, Waltham, MA, United States) and NanoDrop One spectrophotometer (Thermo Fisher Scientific) were used to quantify total RNA, after which the library was constructed. The library for polymerase chain reaction product purification by paired-end libraries was synthesized using the mRNA-seq Lib Prep Kit for Illumina (ABclonal, Wuhan, China) following the sample preparation guide. Libraries were quantified using a Qubit® 3.0 Fluorometer (Thermo Fisher Scientific) and validated using an Agilent 2100 Bioanalyzer (Agilent Technologies) to calculate the molar concentration and insert size. Clusters were generated using the cBot user guide and sequenced using an Illumina NovaSeq 6000 system (Illumina). Library construction and sequencing were performed by Sinotech Genomics Co. Ltd.

Hisat2 (2.1.0) was used to map the paired-end sequence files (fastq) to the reference genome (GRCh38.91). The output sequencing alignment/map files were converted into binary alignment/map files and sorted using SAM tools (v1.7). Gene abundance was expressed as fragments per kilobase of exons per million reads mapped (FPKM). StringTie software was used to count the fragments within each gene, and the TMM algorithm was used for normalization (https://www.ncbi.nlm.nih.gov/COG/). Finally, the FPKM value of each gene was calculated. EdgeR software was used to conduct differential expression analysis of the mRNA[25].

Statistical analysis

Data were analyzed using SPSS software (version 18.0; SPSS Inc., Chicago, IL, United States). Intergroup comparisons of continuous variables were conducted using Student's t-test, and categorical variables were analyzed using Pearson's chi-

square test. Differentially methylated CpG positions were identified using ChAMP. Δβ was calculated as the difference of mean β-values between responders and non-responders. We set the criteria for differential methylation positions (DMPs) as the calling significance of an absolute change in Δβ-value between groups ($|\Delta\beta| \geq 0.06$ and $q < 0.05$). Differentially expressed mRNAs were defined as $|\log2(FC)| > 1$ and $q < 0.05$. To identify genes with the same function and pathway in DNA methylation and gene expression profiling, we performed gene ontology (GO) (http://geneontology.org/) analysis for biological processes, cellular components, and molecular function, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis (http://www.kegg.jp/) for differentially methylated and expressed genes. For all statistical analyses, a two-tailed p-value < 0.05 indicated statistical significance. The q-value cut-off of 0.05 was corrected using the Benjamini–Hochberg method for multiple hypotheses[26].

RESULTS

Demographic and clinical characteristics

PD samples were divided into 13 responders (6 men and 7 women; 33.54 ± 11.64 years old) and 17 non-responders (8 men and 9 women; 33.88 ±9.65 years old) at 4 wk. No statistically significant differences were found between the responders and non-responders in terms of sex ($\chi^2 = 0.002$, $p > 0.05$) or age ($t = -0.088$, $p > 0.05$). There were 4 smokers (30.8%) and 9 nonsmokers (69.2%) in the responder group, and 5 smokers and 12 nonsmokers in the non-responder group. The number of drinkers and nondrinkers among the responders was 3 (23.1%) and 10 (76.9%) in the responder group, and 5 drinkers and 12 nondrinkers in the non-responder group. No statistically significant group difference was observed in terms of smoking and drinking ($\chi^2 = 0.006$, 0.151; $p > 0.05$). In addition, the average PDSS total score was 13.08 ± 4.25 in responders and 14.94 ± 3.25 in non-responders at the start of treatment, and no statistically significant group difference was observed ($t = -1.363$, $p > 0.05$). The average PDSS total score for responders was 4.54 ± 2.11, which was significantly lower than that for non-responders 10.35 ± 2.00 after 4 wk of treatment ($p < 0.001$).

Differential methylation analysis

Compared with non-responders, there were 701 DMPs ($|\Delta\beta| \geq 0.06$, $q < 0.05$), and the hyper- and hypomethylated CpG sites were 511 (72.9%) and 190 (27.1%), respectively (Supplementary Table 1). The distribution of DMPs in the CpG islands was as follows: N-shore (34.6%), S-shore (24.5%), N-shelf (16.5%), island (14.4%), and S-shelf (10.1%). These DMPs in different regions of the gene were in the following order: Body region (64.4%), transcriptional start site (TSS) 1500 (15.3%), 5′-untranslated region (UTR) region (12.5%), 1st Exon (3.4%), TSS 200 (3.1%), and the 3′-UTR region (1.3%). According to the University of California Santa Cruz annotation, 437 unique genes were identified, including 311 hypermethylated and 122 hypomethylated genes; the coexistence of hyper- and hypomethylation sites was found in four genes (Supplementary Table 2).

Enrichment analysis of differentially methylated genes

GO analysis revealed distinct functional categories for the associated genes, and approximately 226 biological processes, 14 cellular components, and 22 molecular functions were identified in differentially methylated genes ($q < 0.05$). Figure 1 shows the top 30 GO annotations for the differentially methylated genes. KEGG analysis showed that these differentially methylated genes were involved in 43 significant pathways ($p < 0.05$). However, no statistically significant pathways were found after adjusting using the Benjamini–Hochberg method ($q > 0.05$) (Supplementary Table 3).

Differential mRNA expression analysis

Compared with non-responders, there were 59 differential transcripts after adjusting using the Benjamini–Hochberg method, of which 20 were downregulated and 39 were upregulated ($q < 0.05$) (Figure 2). After the data were analyzed using the screening procedure, the results of mRNA sequencing showed that 132 differentially expressed genes were identified ($p < 0.05$). However, no statistically significant group differences between responders and non-responders were observed after adjusting using the Benjamini–Hochberg method ($q > 0.05$) (Supplementary Table 4).

DISCUSSION

DNA methylation plays an important role not only in the diagnosis of diseases but also in the prediction of efficacy[16, 27]. In this study, a pilot investigation of genome-wide DNA methylation in the early response to antidepressants in patients with PD was conducted using the Illumina 850k BeadChip. To our knowledge, this is the first genome-wide DNA methylation study of the treatment response to escitalopram in PD. According to the screening criteria for differential methylation sites, 701 DMPs were screened among responders and non-responders in patients with PD, and these DMPs were located within 437 unique genes. Similarly, one study assessed genome-wide DNA methylation using the Infinium MethylationEPIC BeadChip in patients with MDD for escitalopram treatment response. They identified 2571 significant DMPs, and 303 DMPs with an absolute change in Δβ-value between groups larger than 0.2[28]. These findings indicate that DMPs are potential peripheral predictors of antidepressant treatment response, and present an important opportunity to improve symptoms through prediction of medication response. Not only that, there is also some emerging evidence to suggest that PD patients have aberrant DNA methylations[29]. Psychiatry as a medical discipline, a diagnosis identifying a disorder should lead to an effective therapy[30]. Hence, epigenetic factors contributing to antidepressant

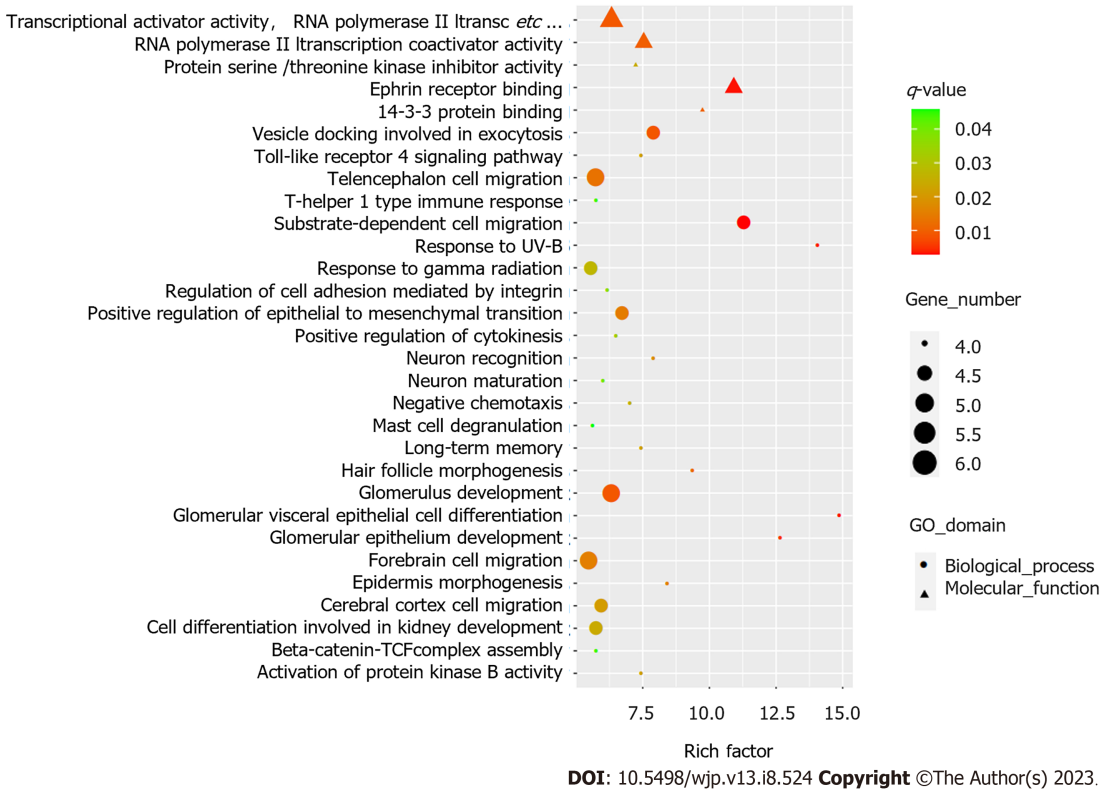

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Figure 1 Top 30 of gene ontology enrichment in differentially methylated genes. GO: Gene ontology.

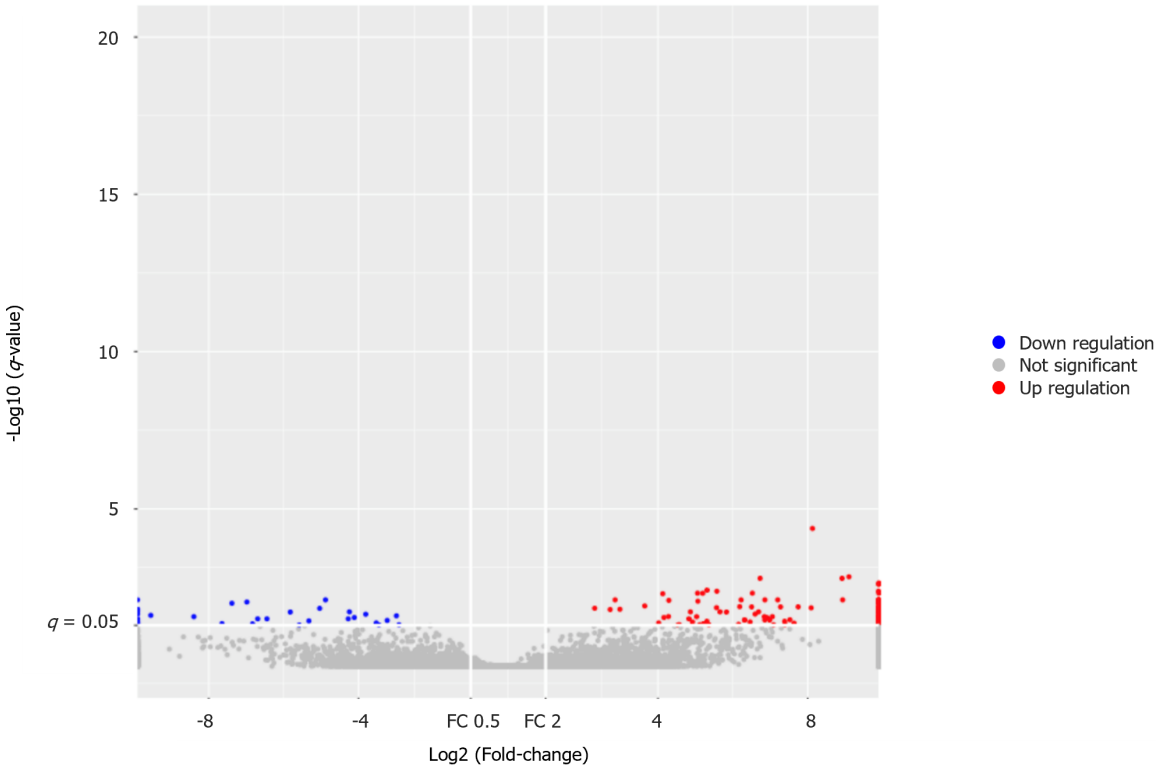

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Figure 2 Differential transcripts between responders and non-responders.

response will be a unique and promising opportunity to implement personalized medicine in PD treatment. In addition, in the present study, most DMPs with an absolute change in value between groups were lower than 0.1. Furthermore, Ju *et al*[28] found that many DMPs showed very small differences in methylation (Δβ < 0.5%), making it difficult to fully

explain efficacy prediction from a single CpG site. The treatment efficacy may be largely determined by the combined effects of multiple loci.

Notably, the current study identified 10 DMPs with an absolute change in Δβ-value larger than 0.2 ($|\Delta\beta| \geq 0.2$) between groups, and these genes included *HLA-DPB1*, *HLA-DPA1*, *PDE1A*, *COL23A1*, *RUFY4*, *FRMD5*, and *SOHLH1*. For example, the *HLA-DPB1* site (cg12865025) is located in the TSS 1500 region. The major histocompatibility complex class II molecule consists of non-covalently associated alpha and beta chains, and this class II molecule is a heterodimer consisting of an alpha (DPA) and a beta chain (DPB)[31]. *HLA-DPA1* and *HLA-DPB1* are expressed on the surfaces of antigen-presenting cells; they play a central role in the adaptive immune system[32] and are associated with the pathophysiology of psychiatric disorders[17]. In recent years, increasing evidence has suggested that aberrations in immune-related pathways contribute to the pathophysiology and prediction of treatment responses in patients with PD [33,34]. Moreover, escitalopram led to a decrease in immune system activation[35], augmented tumor necrosis factor-peripheral secretion, induced faster kinetics of interleukin-1β secretion[36], and decreased Interleukin-17 levels[37]. Therefore, immune-related pathways may play an important role in the response to antidepressants in patients with PD. However, whether these DMPs can be used as molecular markers needs to be verified in larger samples.

In this study, functional enrichment analysis of differentially expressed genes was performed. GO analysis identified 262 GO terms in differentially methylated genes. Notably, the top 30 GO annotations, such as neuron recognition, neuron maturation, and cerebral cortex cell migration, may be associated with the treatment response. These enriched genes, including *DAB1*, *NRP1*, *DIXDC1*, *ROBO1*, *PEX5*, *APP*, *ANKS1A*, *EDNRB*, *BCL2*, and *NTM*, play central roles in brain development, neuronal remodeling, neurite outgrowth, and adhesion. For example, antidepressants such as citalopram increase *APP* secretion in primary rat neuronal cultures[38]. In addition, previous findings suggest that citalopram reduces mutant *APP*, Aβ, and mitochondrial toxicities and may have a protective role against mutant *APP* and Aβ-induced injuries in patients with depression, anxiety, and Alzheimer's disease[39]. In addition, these genes have a potential role in the development of many neuropsychiatric diseases. For example, a previous study found that *Dab1* knockout mice exhibited behavioral abnormalities, including hyperactivity, decreased anxiety-like behavior, and impaired working memory[40]. Hence, these differentially methylated genes in the GO terms may be involved in the pathophysiology and therapeutic response in PD, and the functions of these genes need further exploration. Further studies are needed to explore whether differential methylation in peripheral blood is similar to that in the brain.

Few studies have explored the association between gene expression and the prediction of therapeutic response in patients with PD. In this study, mRNA sequencing was compared between responders and non-responders among patients with PD. Unfortunately, no statistically significant group differences were found in differentially expressed genes. Furthermore, no candidate genes were identified based on integrative analysis of differential DNA methylation and expression. This may be due to the following reasons. First, the sample size was small. The different clinical features of patients with PD are closely related to the heterogeneity of heredity. Second, the use of whole blood, which is a mixed cell type sample, may limit the identification of mRNA expression changes. Finally, gene expression is affected by many factors, such as environmental and other epigenetic factors, especially non-coding RNA, which represents a promising source of peripheral biomarkers of antidepressant responses[41]. Ultimately, it is likely that combinations and not individual biomarkers will have the greatest utility in predicting antidepressant responses. In the future, researchers should integrate multiple types of information, including genetic, epigenetic, and gene expression data, to identify the most meaningful panel of biomarkers.

CONCLUSION

In conclusion, this preliminary study showed that DMPs may be associated with an early response to antidepressants in patients with PD. However, the results of our study should be considered in light of the following limitations. Since this is the first study to investigate genome-wide DNA methylation and gene expression in the prediction of early response to antidepressants in PD, it would be valuable to replicate our findings in a larger cohort. Furthermore, these DMPs must be verified using larger sample sizes. Lastly, it is necessary to test the association between treatment outcomes and changes in DNA methylation and gene expression from pre- to post-treatment with a long-term follow-up.

ARTICLE HIGHLIGHTS

Research background

Selective serotonin reuptake inhibitors are currently considered the first-line treatment for panic disorder (PD). However, not all patients benefit from the antidepressant therapy.

Research motivation

No genome-wide methylation studies or mRNA sequencing have been conducted to identify early response biomarkers in patients with PD.

Research objectives

To compare genome-wide methylation and gene expression patterns between responsive and non-responsive patients with PD after 4 wk of escitalopram treatment.

Research methods
Thirty patients with PD were enrolled in this study (responders = 13; non-responders = 17). All patients were assessed using the PD Severity Scale-Chinese version before and after treatment. The Illumina Infinium MethylationEPIC (850k) BeadChip for genome-wide methylation screening and mRNA sequencing was used in all patients with PD.

Research results
A total of 701 differentially methylated positions (DMPs) were found between responders and non-responders ($|\Delta\beta| \geq 0.06$, $q < 0.05$), and the hyper- and hypomethylated CpG sites were 511 (72.9%) and 190 (27.1%), respectively. Relative to non-responders, there were 59 differential transcripts, of which 20 were downregulated and 39 were upregulated ($q < 0.05$).

Research conclusions
This preliminary study showed that DMPs might be associated with the treatment response to escitalopram in PD, however, these DMPs need to be verified in large samples.

Research perspectives
DNA methylation contributing to antidepressant response will be a unique and promising opportunity to implement personalized medicine in PD treatment.

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FOOTNOTES

Author contributions: Zou ZL was responsible for methodology, writing-original draft, funding acquisition, participants recruitment, blood sample collection, and data curation; Zhang Y was responsible for data curation, formal analysis; Huang YL and Wang JY was responsible for participants recruitment; Zhou B and Chen HF was responsible for conceptualization and participants recruitment.

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Informed consent statement: All individuals provided written informed consent prior to the initiation of study procedures.

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

Data sharing statement: The data used and analyzed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Effects of surgical treatment modalities on postoperative cognitive function and delirium in elderly patients with extremely unstable hip fractures

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Abstract

BACKGROUND

As the perioperative risk of elderly patients with extremely unstable hip fractures (EUHFs) is relatively high and therapeutic effect is not satisfactory, new therapeutic strategies need to be proposed urgently to improve the efficacy and clinical outcomes of such patients.

AIM

To determine the influence of two surgical treatment modalities on postoperative cognitive function (CF) and delirium in elderly patients with EUHFs.

METHODS

A total of 60 elderly patients consecutively diagnosed with EUHF between September 2020 and January 2022 in the Chongqing University Three Gorges Hospital were included. Of them, 30 patients received conventional treatment (control group; general consultation + fracture type-guided internal fixation), and the other 30 received novel treatment (research group; perioperative multidisciplinary treatment diagnosis and treatment + individualized surgical plan + risk prediction). Information on hip function [Harris hip score (HHS)], perioperative risk of orthopedic surgery [Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM)], CF [Montreal cognitive assessment scale (MoCA)], postoperative delirium [mini-cognitive (Mini-Cog)],

adverse events (AEs; internal fixation failure, infection, nonunion, malunion, and postoperative delirium), and clinical indicators [operation time (OT), postoperative hospital length of stay (HLOS), ambulation time, and intraoperative blood loss (IBL)] were collected from both groups for comparative analyses.

RESULTS

The HHS scores were similar between both groups. The POSSUM score at 6 mo after surgery was significantly lower in the research group compared with the control group, and MoCA and Mini-Cog scores were statistically higher. In addition, the overall postoperative complication rate was significantly lower in the research than in the control group, including reduced OT, postoperative HLOS, ambulation time, and IBL.

CONCLUSION

The new treatment modality has more clinical advantages over the conventional treatment, such as less IBL, faster functional recovery, more effectively optimized perioperative quality control, improved postoperative CF, mitigated postoperative delirium, and reduced operation-related AEs.

Key Words: Extremely unstable hip fracture; Elderly; Multidisciplinary treatment; Cognitive function; Postoperative delirium

Core Tip: Characterized by severe fragmentation, extreme instability, and treatment-refractory, extremely unstable hip fractures (EUHFs) in the elderly population carry a higher perioperative risk. Given the unsatisfactory treatment outcomes of EUHFs in the elderly, there is an urgent need to develop new therapeutic strategies to improve the efficacy and clinical outcomes in these patients, thus providing a guarantee for their life, health, and quality of life.

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INTRODUCTION

Extremely unstable hip fractures (EUHFs) account for approximately one-fourth of all hip fractures, mainly including Garden grade III and IV fractures of the femoral neck, A2 and A3 intertrochanteric femur fractures, and Seinsheimer type III and IV subtrochanteric femoral fractures, characterized by severe fragmentation, extreme instability, and treatment-refractory[1,2]. EUHF has a predilection for two groups of people: Young people who have suffered major trauma and elderly people with severe osteoporosis and minor trauma[3]. Elderly patients with EUHF have a higher perioperative risk due to their poorer physical conditions than young and middle-aged people and the high likelihood of comorbidities such as hyperlipidemia, hyperglycemia, hypertension, and other internal diseases[4]. Clinically, the surgical treatment modality for elderly patients with EUHF is selected mainly on the fracture type, which not only leads to unsatisfactory treatment outcome but may also cause postoperative cognitive dysfunction in > 40% and postoperative delirium in 5%-61% of patients, severely affecting their quality of life (QoL)[5,6]. Therefore, it is imperative to develop novel treatment strategies to improve the efficacy and clinical outcomes in elderly patients with EUHF and to provide a guarantee for their life, better health, and improved QoL.

Multidisciplinary treatment (MDT) is a diagnosis and treatment model that gathers the backbones of EUHF-related departments, such as geriatrics, critical medicine, anesthesiology, mental health, and rehabilitation medicine, to tailor personalized examination and treatment plans for patients to improve patient diagnosis and treatment experience and enhance treatment efficacy[7-9]. A randomized controlled trial including elderly patients with hip fractures also observed significant improvement in postoperative clinical outcomes using MDT, which suggested that MDT has great application potential in elderly patients with EUHF[10]. On the other hand, anatomic reduction, internal fixation, and effective control of postoperative adverse events (AEs) for EUHFs are the keys to successful surgery due to the vulnerability to fractures of the area involved and the complexity and involvement of the surrounding muscle groups[11,12]. We believe that individualized customization + fracture type co-determined internal fixation is a feasible and safe program, and risk prediction and advance treatment through Mini-Cog plus orthopedic Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) scale assessment can further help minimize the surgical risks.

To test our conjecture and supplement the evidence-based new treatment model (MDT diagnosis and treatment + individualized surgical plan + risk prediction) still lacks, this study compared the clinical effects of the two surgical treatment modalities through a clinical cohort study to optimize and scientifically guide the clinical treatment.

MATERIALS AND METHODS

General data

This study comprised 60 elderly patients diagnosed consecutively with EUHF in the Chongqing University Three Gorges Hospital between September 2020 and January 2022. Of 60, 30 patients were treated using the conventional treatment model of general consultation plus fracture type-guided internal fixation (control group), and the other 30 patients received a new treatment model of perioperative MDT diagnosis and treatment + individualized surgical plan + risk prediction (research group). The two patient groups had similar baseline data ($P > 0.05$), which was clinically comparable.

Inclusion and exclusion criteria for patient enrollment

Patients diagnosed with extremely unstable femoral intertrochanteric fractures (Garden grade III or IV fractures of the femoral neck, A2 or A3 intertrochanteric femur fractures, or Seinsheimer type III or type IV subtrochanteric femoral fractures), but not old or pathological fractures, using computed tomography, magnetic resonance imaging, and other imaging examinations[13,14], with no severe osteoporosis, t value ≥ -2.5, normal communication and cognitive abilities, and active cooperation were included.

The exclusion criteria were as follows: Other hip diseases; serious nerve; vascular or muscle injuries; other joint diseases; femoral head necrosis; serious infections; diseases such as coagulation dysfunction, cardiopulmonary disease, and renal failure; drug and alcohol addiction; and history of severe trauma around the hip joint.

Treatment protocols

The control group received conventional treatment, with the following specific measures: Post-admission general consultation was provided to the patients and relevant examinations and treatment were further conducted according to the consultation. The patient's underlying diseases were stabilized preoperatively; however, another preoperative evaluation was conducted by the anesthesiologist. The surgical protocol was selected depending on the patient's fracture type. After surgery, the patient's vital signs, mental state, food intake, blood routine, biochemical indexes, drainage volume, and cardiopulmonary function were obtained, and bilateral lower limb vascular ultrasonography was performed. Prophylactic antibiotics were used within 24 h after surgery, and anticoagulant therapy composed of low molecular weight heparin and rivaroxaban was routinely given. Postoperatively, the affected limb was raised according to the patient's fracture type, surgical condition, and general condition. In addition, the patient was instructed to perform quadriceps isometric contraction and ankle pump exercises. Those with good wound healing, no hip pain, sound mind, good appetite, no serious complications, and no serious abnormalities in various laboratory indexes were discharged.

The research group adopted a new treatment model, perioperative MDT diagnosis and treatment + individualized surgical plan + risk prediction. Details of the treatment methods are described as follows: (1) After admission, an MDT team, which was led by orthopedic surgeons and composed of professional backbones with intermediate titles or above in geriatrics, critical medicine, anesthesiology, mental health, rehabilitation medicine, and other related departments, was set up. The MDT team evaluated the patients' specific conditions, formulated personalized examination and treatment plans, and opened green channels to shorten the waiting time for examinations. In addition, the mental state of the patients was adjusted to actively prepare them for surgery, and the time between admission and operation was shortened as much as possible; (2) A surgical protocol was jointly developed based on each patient's treatment and fracture type, as assessed by the MDT team. If the hemoglobin count was > 90 g/L after blood transfusion, with no hypertension, lower limb deep venous thrombosis (except for those undergoing inferior vena cava filter placement), preoperative delirium, and serious basic diseases, the internal fixation scheme was determined according to the fracture type. For those with preoperative hypoproteinemia, moderate-to-severe anemia that cannot be corrected, severe underlying diseases, and delirium, among others, the internal fixation method was comprehensively considered in combination with the fracture type, and proximal femoral locking plate (PFLP) fixation was performed when necessary; and (3) During the perioperative period, patients were assessed using the Mini-Cog and orthopedic POSSUM scales for delirium and risk prediction, respectively. Patients who were not eligible for surgery at the time were treated by relevant specialists and re-evaluated after their condition improved. The post-surgical patients were re-evaluated by the MDT team, and timely and effective treatment was given if necessary. Those with multiple medical diseases and more serious conditions were admitted to the intensive care unit after the operation. In addition, mental health practitioners assessed the patients' mental state before and after surgery to better guide the treatment. Moreover, rehabilitation physicians instructed patients to exercise to improve muscle strength and joint range of motion and assisted with early ambulation. Other routine diagnoses, treatments, and discharge standards after the operation were the same as in the control group.

Detection indicators

Hip function: Patients' hip function was assessed using the Harris Hip Score (HHS) before and 6 mo after surgery for pain (0-44 points), function (0-47 points), deformity (0-4 points), and range of motion (0-5 points) components, with a total score of 100 points. A higher score indicated a better hip functional recovery.

Preoperative risk assessment: The orthopedic POSSUM scoring system, which consists of 12 variables forming the physiological assessment (score range 12-96) and 6 variables forming the operative severity assessment (score range 6-48), was used to evaluate the surgical risk of patients. A higher score suggested a greater risk.

Cognitive function assessment: Using the Montreal Cognitive Assessment Scale (MoCA; score range 0-30), the patients' cognitive function (CF) was assessed from 11 items in 8 knowledge fields (memory, language, attention and concentration, executive functions, visuospatial skills, abstraction, calculations, and orientation). In addition, the patients'

Table 1 Analysis of comparability of general data between the two groups

Categories	Control group (*n* = 30)	Research group (*n* = 30)	χ^2 value	*P* value
Sex			0.067	0.796
Male	14 (46.67)	15 (50.00)		
Female	16 (53.33)	15 (50.00)		
Age (yr)	63.20 ± 5.32	62.40 ± 6.04	0.544	0.588
Fracture site			0.617	0.432
Left	11 (36.67)	14 (46.67)		
Right	19 (63.33)	16 (53.33)		
Hypertension			0.635	0.426
Yes	17 (56.67)	20 (66.67)		
No	13 (43.33)	10 (33.33)		
Diabetes			0.373	0.542
Yes	8 (26.67)	6 (20.00)		
No	22 (73.33)	24 (80.00)		

intelligence was assessed using the Mini-Cognitive (Mini-Cog) scale (score range 0-5). Scores on both scales were proportional to CF.

Incidence rate of AEs: AEs that occurred during treatment, such as internal fixation failure, infection, nonunion, malunion, and postoperative delirium, were observed and recorded in all patients, and the incidence rate was calculated.

Clinical indicators: Clinical indicators, including operation time (OT), postoperative hospital length of stay (HLOS), ambulation time, and intraoperative blood loss (IBL), were recorded and compared.

Statistical analysis

All statistical analyses were performed using SPSS 20.0. The mean ± SEM was used to describe continuous variables, and the *t*-test was used for comparison between groups. Categorical variables were expressed as percentages, and the χ^2 test was used for intergroup comparison. $P < 0.05$ was considered statistically significant.

RESULTS

General information

A comparative analysis of patient general data, such as sex, age, fracture site, hypertension, and diabetes, showed clinical comparability between both groups ($P > 0.05$; Table 1).

Hip joint function

The patients' hip joint function was evaluated by assessing the pain, function, range of motion, and deformity components of the HHS. The analysis showed no significant intergroup difference in HHS scores before and after intervention ($P > 0.05$). However, the intragroup comparison revealed markedly elevated HHS scores in both groups after intervention ($P < 0.05$) (Figure 1).

Orthopedic POSSUM scale scores

After the analysis using the orthopedic POSSUM scale, it was found that the preoperative physiological and operative severity scores of the research group were significantly reduced as compared to the control group ($P < 0.05$) (Figure 2).

CF

A comparative analysis of patients' CF using the MoCA and Mini-Cog showed no significant difference in both scores between groups prior to the intervention ($P > 0.05$). After the intervention, the MoCA score was significantly reduced in both groups ($P < 0.05$), with an even higher score in the research group ($P < 0.05$). In terms of the Mini-Cog score, a significant decrease was observed in the control group ($P < 0.05$) as opposed to a non-significant decrease in the research group after intervention ($P > 0.05$); however, comparatively, the score remained significantly higher in the research group ($P < 0.05$) (Figure 3).

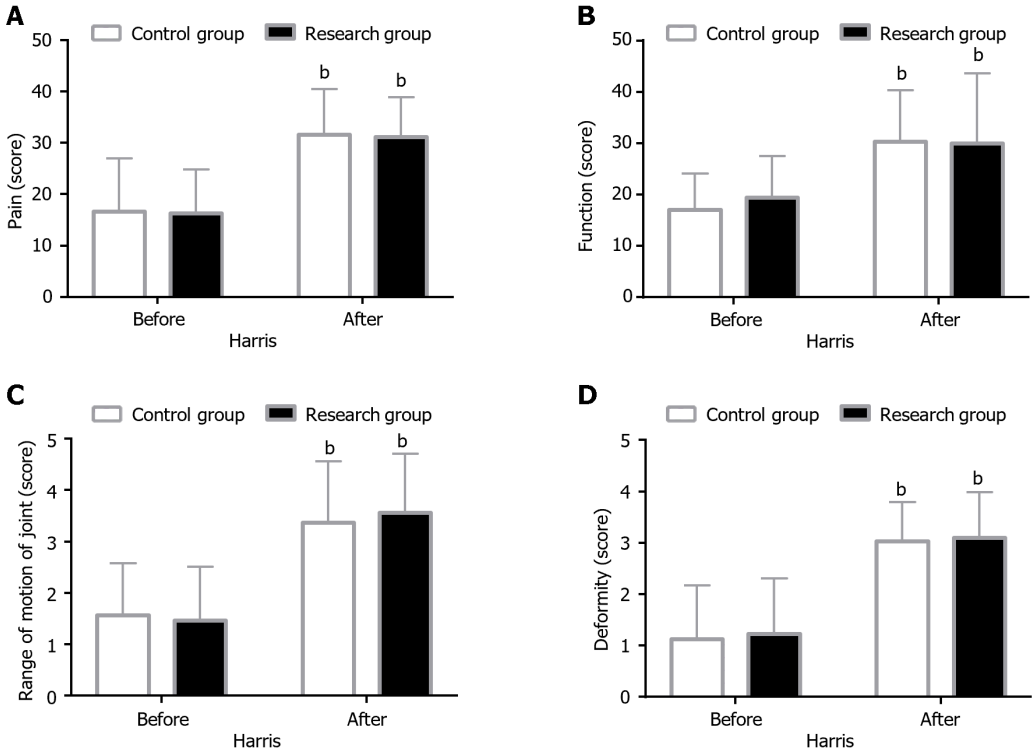

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Figure 1 Hip function. A: There are no significant differences between the research and control groups in pre- and post-interventional pain scores; however, elevated pain scores relative to the pre-interventional values are observed in both groups; B: There are no significant differences between the two groups in pre- and post-interventional function scores; however, elevated function scores relative to the pre-interventional values are observed in both groups; C: There are no significant differences between the two groups in pre- and post-interventional joint range of motion (ROM) scores; however, elevated joint ROM scores relative to the pre-interventional values are observed in both groups; D: There are no significant differences between the two groups in pre- and post-interventional deformity scores; however, elevated deformity scores relative to the pre-interventional values are observed in both groups. $^{b}P < 0.01$ *vs* before intervention. ROM: Range of motion.

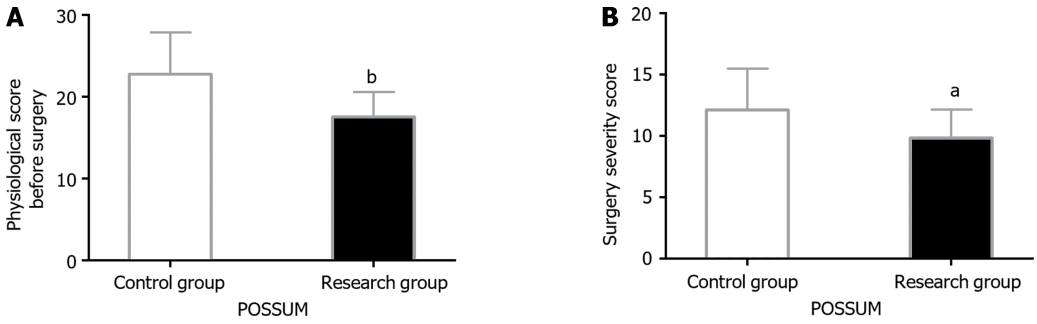

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Figure 2 Orthopedic Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity scale scores. A: Preoperative physiological scores are significantly lower in the research group than in the control group; B: Surgical severity scores are lower in the research group than in the control group. $^{a}P < 0.05$ and $^{b}P < 0.01$ *vs* control group. POSSUM: Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity.

AEs

According to the statistics on internal fixation failure, infection, nonunion, malunion, and postoperative delirium, the total incidence of AEs was found to be significantly lower in the research than in the control group ($P < 0.05$; Table 2).

Clinical indexes

The measurement of clinical indexes revealed less OT, postoperative HLOS, and IBL and early ambulation in the research group than in the control group ($P < 0.05$) (Figure 4).

Table 2 Adverse events

Events	Control group (n = 30)	Research group (n = 30)	χ^2 value	P value
Internal fixation failure	1 (3.33)	1 (3.33)	-	-
Infection	2 (6.66)	1 (3.33)	-	-
Nonunion	2 (6.66)	1 (3.33)	-	-
Malunion	2 (6.66)	0 (0.00)	-	-
Postoperative delirium	3 (10.00)	0 (0.00)	-	-
Total	10 (33.33)	3 (10.00)	4.812	0.028

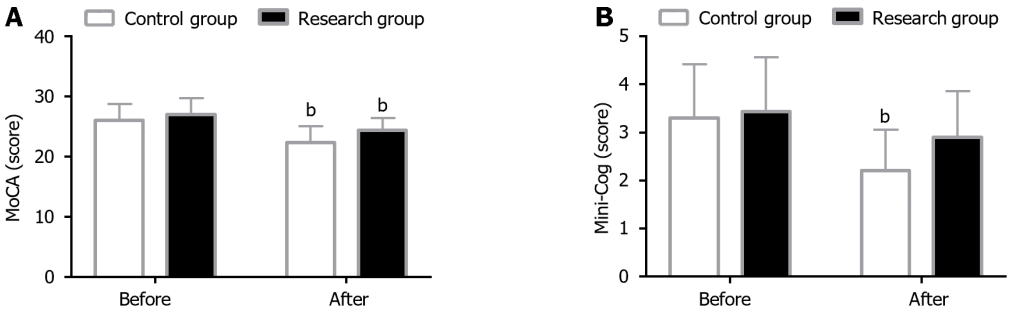

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Figure 3 Cognitive function. A: Montreal cognitive assessment scale scores are markedly reduced in the research group but remained higher than the control group after intervention; B: Mini-Cog scores are slightly altered in the research group but remained higher than in the control group after intervention. $^bP < 0.01$ *vs* before intervention; $P < 0.05$ *vs* control group. MoCA: Montreal cognitive assessment scale; Mini-Cog: Mini-Cognitive.

DISCUSSION

Conventional treatment is less effective in the treatment of elderly patients with EUHFs, and surgery is currently the treatment of choice to help patients regain their independence, including work ability, faster after injury[15]. In addition, the general consultation model adopted in conventional treatment has some shortcomings, such as delayed treatment time due to repeated preoperative consultation and examination, which leads to various complications in some patients waiting for surgery, including loss of the optimal timing for surgery[16]. Given the above problems, developing effective solutions to optimize the diagnosis and treatment experience of elderly patients with EUHF is imperative.

In this study, the new treatment model was based on MDT diagnosis and treatment + individualized surgical plan + risk prediction, with holistic sequential trauma treatment as the concept[17]. However, the conventional treatment model included general consultation + fracture type-guided internal fixation as the main program and local trauma theory as the main guidance[18]. Herein, significantly enhanced hip joint function, reflected in significantly elevated HHS scores in pain, function, range of motion, and deformity dimensions, was observed in both cohorts after surgery. However, no significant intergroup differences were observed, which suggested that the two surgical treatment modalities had similar effects in elderly patients with EUHF. This may be attributed to the guiding exercise for hip functional rehabilitation administered to patients in both treatment protocols. According to Wu *et al*[19], the application of MDT in combination with perioperative management in elderly patients with intertrochanteric fractures not only significantly reduced perioperative symptoms but also effectively facilitated postoperative rehabilitation and long-term improvement of hip function, similar to our findings. Surgical treatment of hip fractures is known to be extremely life-threatening for elderly patients, and the prediction and evaluation of surgical risk based on individual differences can be helpful to improve surgical outcomes[14,20]. Therefore, in this study, we used orthopedic POSSUM and Mini-Cog scales to predict the surgical risk and postoperative delirium in elderly patients with EUHF. The data from the orthopedic POSSUM scale showed that the research group had lower preoperative physiological and operative severity scores than the control group, indicating reduced surgical risk under the intervention of the new treatment model. This may be attributed to the preoperative prediction, accurate assessment, and advanced management of complications in patients under the new treatment model. Previous studies have shown that the POSSUM scale has a certain application value in the risk assessment of hip fracture surgery in elderly patients. Risk management based on this scale, combined with the cooperation of the MDT team, can help reduce the mortality and readmission rates of elderly patients with fractures in the perioperative period and improve their functional outcomes[21,22]. Regarding the MoCA and Mini-Cog scores, the post-interventional scores in the research group were notably higher than the post-interventional values in the control group, indicating that the new treatment model can help prevent postoperative cognitive impairment and delirium in such patients. Postoperative cognitive dysfunction and delirium, which are common postoperative complications in elderly patients with hip fractures, have been associated with a significant increase in postoperative serum S100A12 levels[23,24]. Similarly, Zhu *et al*[25] suggested that perioperative geriatric comprehensive assessment for elderly patients with hip fractures can not

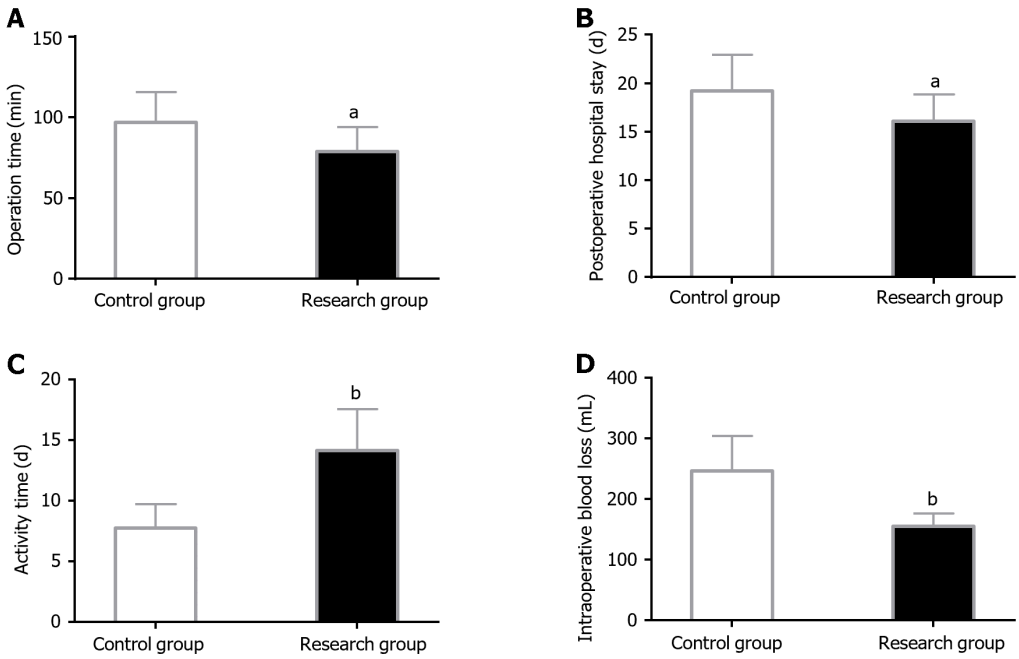

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Figure 4 Clinical indicators. A: Operation time is significantly shorter in the research group than in the control group; B: Postoperative hospital length of stay is significantly shorter in the research group than in the control group; C: Activity time is significantly longer in the research group than in the control group; D: Intraoperative blood loss is statistically less in the research group than in the control group. [a]$P < 0.05$ and [b]$P < 0.01$ *vs* control group.

only shorten the preoperative waiting time and total hospital stay compared with conventional consultation but also reduce the risk of postoperative delirium, in line with our findings.

Among various AEs, the incidence of internal fixation failure, infection, nonunion, malunion, and postoperative delirium was significantly lower in the research than in the control group, suggesting that it is safe for elderly patients with EUHF to receive the new treatment. The aforementioned prevention of postoperative cognitive impairment and delirium helps to avoid prolonged bed rest, subsequently reducing the risk of bedsores and pulmonary infection, including the incidence of postoperative AEs and mortality[26]. In addition, the orthopedic POSSUM scale was introduced in this study for preoperative comprehensive assessment, allowing for causative or symptomatic treatment of the problems found in the evaluation to significantly reduce postoperative AEs, which also explains the above results [27]. Finally, we found that patients in the research group had more clinical advantages than those in the control group in terms of OT, postoperative HLOS, ambulation time, and IBL, suggesting that the new treatment model can shorten treatment time, promote patients' rehabilitation, and improve surgical safety. This may be attributed to the emphasis on local trauma and the neglect of overall trauma in the conventional treatment model, which often leads to long OT, excessive bleeding, and more postoperative complications[28,29]. On the contrary, the new treatment model links the difficulty of anatomical reduction with the operation tolerance time and anesthesia mode and applies traditional PFLP fixation to a small number of patients with poor basic conditions. PFLP fixation, a simple clinical procedure, can not only reduce the interference to the blood supply at the fracture end but also increase the stability and strength of the nail-bone combination, which is conducive to shortening the OT while maintaining a certain therapeutic effect[30]. In a study by Rui *et al*[31], the new treatment model formulated by the MDT team for hip fractures in the elderly is beneficial to shorten the OT and postoperative HLOS, in line with our findings.

CONCLUSION

The new treatment model using MDT diagnosis and treatment + individualized surgical plan + risk prediction was superior to the conventional treatment model of general consultation + fracture type-guided internal fixation in clinical efficacy to a certain extent. The main clinical advantages of the novel treatment model were lower surgical risks, lower incidence of postoperative AEs, more effectively accelerated patient recovery, and prevention against postoperative cognitive dysfunction and delirium, which can improve the treatment efficacy and experience of elderly patients with EUHF and provide more accurate evidence to guide clinical application.

ARTICLE HIGHLIGHTS

Research background

Given the current high perioperative risk of extremely unstable hip fractures (EUHFs) in elderly patients and the unsatisfactory treatment outcomes, there is an urgent need to propose new treatment strategies to treat these patients.

Research motivation

To improve the efficacy and clinical outcome of EUHFs in the elderly, it is necessary to explore and optimize the relevant treatment strategies.

Research objectives

This study focuses on the clinical application effects of two surgical treatment modalities in older adults with EUHFs.

Research methods

First, 60 older adults consecutively diagnosed as EUHFs between September 2020 and January 2022 in the Chongqing University Three Gorges Hospital were selected as the research participants, among which 30 cases in the control group (Con) received conventional treatment (general consultation + fracture type-guided internal fixation) and the other 30 cases in the research group (Res) received novel treatment [perioperative multi-disciplinary treatment (MDT) diagnosis and treatment + individualized surgical plan + risk prediction]. Information on hip function (Harris hip score, HHS), perioperative risk of orthopedic surgery (Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity, POSSUM), CF (Montreal cognitive assessment scale, MoCA), postoperative delirium (mini-cognitive, Mini-Cog), AEs (internal fixation failure, infection, nonunion, malunion, and postoperative delirium), clinical indicators (OT; postoperative hospital length of stay, HLOS; ambulation time; intraoperative blood loss, IBL) were collected from both groups for comparative analyses.

Research results

The HHS scores were similar between both groups. The POSSUM score at 6 mo after surgery was significantly lower in the research group compared with the control group, and MoCA and Mini-Cog scores were statistically higher. In addition, the overall postoperative complication rate was significantly lower in the research than in the control group, including reduced OT, postoperative HLOS, ambulation time, and IBL.

Research conclusions

With comparable efficacy in fracture healing, the new treatment modality has some clinical advantages over the conventional treatment, such as less IBL, faster functional recovery, more effectively optimized perioperative quality control, improved postoperative cognitive function, mitigated postoperative delirium, and reduced operation-related adverse events.

Research perspectives

The novel treatment model of MDT diagnosis and treatment + individualized surgical plan + risk prediction can improve the therapeutic efficacy and experience of elderly patients with EUHFs, providing more accurate evidence to guide the management of EUHFs in clinical practice.

FOOTNOTES

Author contributions: Zhou X and Wang HM contributed to the research design and thesis writing; Zhou X, Chen XH, and Li SH collected and analyzed the data; Zhou X, Li N and Liu F contributed to the data collection; Zhou X and Wang HM overall supervise the study; and all authors contributed to the article and approved the submitted version.

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

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ORIGINAL ARTICLE

Retrospective Study

Nursing model of midwifery and postural and psychological interventions: Impact on maternal and fetal outcomes and negative emotions of primiparas

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Abstract

BACKGROUND

Primiparas are usually at high risk of experiencing perinatal depression, which may cause prolonged labor, increased blood loss, and intensified pain, affecting maternal and fetal outcomes. Therefore, interventions are necessary to improve maternal and fetal outcomes and alleviate primiparas' negative emotions (NEs).

AIM

To discusses the impact of nursing responsibility in midwifery and postural and psychological interventions on maternal and fetal outcomes as well as primiparas' NEs.

METHODS

As participants, 115 primiparas admitted to Quanzhou Maternity and Child Healthcare Hospital between May 2020 and May 2022 were selected. Among them, 56 primiparas (control group, Con) were subjected to conventional midwifery and routine nursing. The remaining 59 (research group, Res) were subjected to the nursing model of midwifery and postural and psychological interventions. Both groups were comparatively analyzed from the perspectives of delivery mode (cesarean, natural, or forceps-assisted), maternal and fetal outcomes (uterine inertia, postpartum hemorrhage, placental abruption, neonatal pulmonary injury, and neonatal asphyxia), NEs (Hamilton Anxiety/Depression-rating Scale, HAMA/HAMD), labor duration, and nursing satisfaction.

RESULTS
The Res exhibited a markedly higher natural delivery rate and nursing satisfaction than the Con. Additionally, the Res indicated a lower incidence of adverse events (*e.g.*, uterine inertia, postpartum hemorrhage, placental abruption, neonatal lung injury, and neonatal asphyxia) and shortened duration of various stages of labor. It also showed statistically lower post-interventional HAMA and HAMD scores than the Con and pre-interventional values.

CONCLUSION
The nursing model of midwifery and postural and psychological interventions increase the natural delivery rate and reduce the duration of each labor stage. These are also conducive to improving maternal and fetal outcomes and mitigating primiparas' NEs and thus deserve popularity in clinical practice.

Key Words: Nursing model of midwifery; Postural intervention; Primipara; Maternal and fetal outcomes; Negative emotions

Core Tip: Primiparas are at high risk for depression during the perinatal period, which can lead to prolonged labor, increased blood loss, and intensified pain that can affect maternal and fetal outcomes. Therefore, it is necessary to give relevant interventions to improve maternal and fetal outcomes and alleviate negative emotions in primiparas.

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INTRODUCTION

Primiparas and multiparas are often at a high risk of experiencing perinatal depression because of the significant physical and psychological burdens they encounter[1]. As reported, the incidence of depression is higher among primiparas than multiparas[2,3]. Clinically, primiparas often develop negative emotions (NEs), such as fear and anxiety, due to severe labor pain caused by inexperience during delivery[4]. Owing to this, mothers may suffer from a lack of strength or improper exertion, leading to prolonged labor, increased blood loss, and intensified pain[5,6]. The type of delivery can also affect maternal and fetal outcomes, with mothers undergoing cesarean section (CS) facing a higher risk of complications[7]. Thus, this study intends to mitigate the NEs of primiparas and improve maternal and fetal outcomes by combining the appropriate nursing model with certain interventions. This study also contributes toward the prevention of maternal complications as well as management optimization during clinical application.

Although routine midwifery and nursing aid primiparas, the quality across medical institutions may vary[8]. There is a need to improve the regulatory effect of routine nursing on maternal NEs[9]. Therefore, our research team adopted the care model of midwifery, a novel model of midwifery nurse practice that prioritizes the psychological and emotional state of mothers and is more humanized[10,11]. In the study on maternal care by Beecher *et al*[12], the improvement of maternal psychological quality under the midwifery responsibility system was demonstrated and its positive effect was affirmed. Besides, Wu *et al*[13] reported on the intervention of primary maternal care, pointing out that combining postural and breathing training under the original nursing model can effectively smoothen the delivery process and improve the outcomes of primiparas.

Currently, there are insufficient studies on the clinical application of the care model of midwifery as well as postural and psychological interventions in primipara nursing management, which is this study's focus. It explores and analyzes the same from the perspectives of delivery mode, maternal and fetal outcomes, NEs, labor duration, and nursing satisfaction. Its ultimate goal is to provide an effective clinical basis for the nursing management of primiparas and improve their delivery experience.

MATERIALS AND METHODS

Study participants

The study participants were 115 primiparas who visited the Quanzhou Maternity and Child Healthcare Hospital between May 2020 and May 2022. The control group (Con; n = 56) was subjected to conventional midwifery and routine nursing; the research group (Res; n = 59) was subjected to the nursing model of midwifery and postural and psychological interventions. Both groups had similar baseline (P > 0.05) and clinical comparability. The inclusion criteria were as follows: Primiparas with full-term pregnancy and normal pelvic diameter after measurement; single pregnancy, normal

fetal presentation, and priority for a vaginal birth; no high-risk maternal complications during pregnancy or pregnancy complications; and normal mental state and verbal communication ability. The exclusion criteria were as follows: Malignancies or organ dysfunction; conditions like nuchal cord, premature rupture of membranes, and amniotic fluid volume abnormality; history of uterine surgery; premature birth or post-term pregnancy; abnormal coagulation function; and autoimmune deficiency.

Methods

The Con was subjected to conventional midwifery and routine nursing. After admission, the midwives on duty provided services, such as routine fetal heart monitoring, maternal skin cleaning, labor process observation, and health guidance. There was no postural intervention during the labor period. The parturient was allowed to choose a comfortable posture, and the midwife delivered the baby after the cervix was fully dilated. Routine nursing measures were also provided.

The Res was subjected to the nursing model of midwifery and postural and psychological interventions. First, one-to-one nursing was provided to each primipara, and a private midwife was there to provide care and management throughout the process of labor preparation and delivery. This not only promoted mutual communication but also facilitated the collection of the primipara's information and the formulation and implementation of nursing strategies, thus improving the efficiency and experience of nursing. The main nursing and management provided by midwives included the following aspects: (1) Prenatal education: Midwives introduced perinatal knowledge to the parturients and informed them of the symptoms they may encounter during the perinatal period and the physiological process of delivery. Through videos and clinical demonstrations, mothers were instructed on pain relief in the first stage of labor through deep breathing, and proper force exertion in the second stage of labor to shorten the labor duration. Additionally, exchanges between multiparas and primiparas were arranged to impart childbirth experience to first-time mothers in order to strengthen their confidence; (2) Psychological intervention: By communicating with the parturients, the midwives evaluated the mothers' potential concerns, depression, fear, and other NEs; they encouraged the mothers to express their worries and provided one-on-one psychological counseling based on the mothers' personality traits and educational level. Furthermore, by enumerating the successful childbirth experiences of other parturients, the midwives enhanced the mothers' confidence in childbirth and relieved their unhealthy psychology; (3) Postural intervention: During the first stage of labor, the parturients were guided to take a free position, with their attention diverted. For mothers with half engagement of non-engagement of fetal presenting part, they were suggested to walk while supporting the belly to speed up the delivery. If the uterine orifice opening was 1-2 cm and the fetus was found to be in an occipital posterior position, the mother was instructed to assume the contralateral prone position during pregnancy, depending on the specific fixed position during pregnancy. During the second stage of labor when the fetal head descended slowly, the mother was instructed to squat according to the maternal situation; (4) Nursing during labor: During labor, the midwife paid close attention to the physical and mental condition of the mother and relieved contraction-induced pain by helping her wipe sweat, massaging the lower abdomen, and expressing encouragement. At the same time, the progress of labor was closely observed. In the case of increased maternal blood loss, uterine contraction weakness, prolonged second labor, fetal distress, and other conditions, the doctor was immediately reported to take timely corresponding measures; and (5) Postpartum care: After the fetus was delivered and processed, it was sent to the mother in time to guide and help early suckling. The newborn was observed in the infant room for two hours and was timely sent back to its mother if there was no abnormality. The midwives also closely observed the vital signs, uterine contraction, and mental state of the postpartum women, especially the amount of postpartum vaginal bleeding, and offered timely interventions when necessary.

Outcome measures

(1) Mode of delivery. The delivery modes of both groups, including CS, natural delivery, and forceps-assisted delivery (FAD), were observed and recorded; (2) Maternal and fetal outcomes. The maternal and fetal outcomes were compared, including uterine inertia, postpartum hemorrhage, placental abruption, neonatal lung injury, and neonatal asphyxia; (3) NEs. Maternal NEs were evaluated using the Hamilton Anxiety/Depression-rating Scale (HAMA/HAMD)[14]. HAMA has 14 assessment items, and HAMD has 24 assessment items; each item of both is graded from 0 to 4, with higher scores indicating more serious anxiety or depression symptoms; (4) Duration of labor. The duration of each stage of labor was recorded for comparative analysis; and (5) Nursing satisfaction. Patients were asked to fill in the self-made nursing satisfaction questionnaire of our hospital (0-100 points) to understand their satisfaction with the nursing services. Higher scores are indicative of better satisfaction, with a score of > 80 points, 60-80 points, and < 60 points representing satisfactory, basically satisfactory, and unsatisfactory, respectively.

Statistical processing and analysis

The number of cases/percentage (n, %) and the mean ± SEM were used to represent categorical and continuous variables, respectively. Among these, the χ^2 test was used to compare categorical data, and the independent sample t-test compared the continuous variables between the groups. In this study, the SPSS18.0 software package was used for statistical analysis, and a minimum significance level of $P < 0.05$ was used throughout.

RESULTS

General data of both groups

Both study groups were comparable in terms of age, gestational age, body mass index, smoking history, drinking history, educational level, and other general data ($P > 0.05$) (Table 1).

Delivery modes in both groups

According to the comparative analysis of the delivery modes (CS, natural delivery, and FAD), the Res had a higher natural delivery rate ($P < 0.05$), a lower CS rate ($P < 0.05$), and a comparable FAD rate than the Con ($P > 0.05$) (Table 2).

Maternal and fetal outcomes in both groups

Evaluating and comparing the maternal and fetal outcomes, such as uterine inertia, postpartum hemorrhage, placental abruption, neonatal lung injury, and neonatal asphyxia indicated that the incidence of adverse maternal and fetal outcomes described above was statistically lower in the Res ($P < 0.05$) (Table 3).

NEs of both groups

The assessment of maternal anxiety and depression using the HAMA and HAMD revealed that both scale scores were similar in the two groups before the interventions, but they significantly declined after corresponding interventions ($P < 0.05$), with even lower scores in the Res compared to the Con ($P < 0.05$) (Figure 1).

Labor duration in both groups

The time spent in the first, second, and third stages of labor was markedly shorter in the Res than the Con ($P < 0.05$) (Figure 2).

Patient satisfaction with nursing in both groups

Patient satisfaction with the care services was assessed using a self-developed nursing satisfaction questionnaire. The satisfaction of the Res was statistically higher compared to the Con (96.61% *vs* 82.14%, $P < 0.05$) (Table 4).

DISCUSSION

Labor is a physiological process a mother undergoes to deliver an infant, which is accompanied by pain and pressure [15]. Providing scientific and reasonable care management for primiparas is therefore of great value to improve their birthing experience and delivery outcomes. The mode of delivery affects not only maternal and infant health, but also the success rate of breastfeeding[16]. Specifically, although CS is devoid of childbirth pain, it is riskier for maternal and infant health compared to normal delivery; it is associated with a higher risk of maternal mortality and postoperative complications[17,18]. The analysis of delivery modes in this study revealed that the Res had a markedly higher natural delivery rate, a lower CS rate, and a comparable FAD rate than the Con, suggesting that the adoption of the nursing model of midwifery along with postural and psychological interventions can significantly improve the natural delivery rate in primiparas. This may be attributed to the postural guidance provided to the Res, which reduced the oppression of the uterus and the friction caused by the rotation of the carcass, thus ensuring natural delivery[19]. Furthermore, the statistics of maternal and fetal outcomes showed that the incidence of adverse events, such as uterine inertia, postpartum hemorrhage, placental abruption, neonatal lung injury, and neonatal asphyxia, was markedly lower in the Res than in the Con. Thus, the nursing model of midwifery along with postural and psychological interventions is conducive to reducing adverse maternal and fetal outcomes. Considering the potential occurrence of the aforementioned adverse events, this novel nursing model pays close attention to these events and entails timely treatment of such conditions throughout the labor process and postpartum care; this explains the low incidence of adverse events in the Res[20]. In the research of Zhang *et al*[21], continuous midwifery services, which also integrate health education, psychological interventions, and labor and postpartum care, not only elevate the natural delivery rate of primiparas but also significantly improve maternal and fetal outcomes, similar to our findings.

Primiparas are prone to anxiety, fear, and other NEs due to their lack of experience in childbirth; this can affect the progress of labor and the smooth delivery, making psychological interventions crucial[22]. In this study, the Res showed lower HAMA and HAMD scores than the Con after the interventions, indicating that the nursing model of midwifery along with postural and psychological interventions can significantly relieve anxiety, depression, and other NEs in primiparas. This may be related to the fact that the nursing model experienced by the Res included psychological interventions and the timely channelization of maternal NEs[23]. In terms of the labor process, the Con spent more time in the first, second, and third stages of labor than the Res, indicating that the labor process of primiparas is smoother when the nursing model of midwifery and postural and psychological interventions are adopted. In this study, the prenatal education in the nursing management model used in the Res provided primiparas with guidance on the possible problems and coping approaches during the labor process, which helps accelerate the progress of labor[24,25]. Finally, the evaluation of the nursing satisfaction questionnaire showed a satisfaction degree as high as 96.61% in the Res, demonstrating that the nursing model along with the interventions is more popular among first-time mothers and advantageous over the conventional model in clinical practice. Based on the one-to-one nursing model, this novel nursing model provides services, such as prenatal education, psychological and postural interventions, labor care, and

Table 1 General data of both groups of primiparas

Factors	Control group (*n* = 56)	Research group (*n* = 59)	χ^2/t	*P* value
Age (years)	26.80 ± 7.23	28.46 ± 7.20	1.233	0.220
Gestational age (weeks)	37.71 ± 1.58	37.90 ± 1.77	0.606	0.546
BMI (kg/m^2)	22.85 ± 2.95	22.70 ± 3.21	0.261	0.795
History of smoking (yes/no)	14/42	11/48	0.682	0.409
History of alcoholism (yes/no)	10/46	16/43	1.408	0.235
Educational level (primary school or junior high school/senior high school/junior college and above)	17/26/13	18/30/11	0.403	0.818

BMI: Body mass index.

Table 2 Delivery modes of both groups, *n* (%)

Categories	Control group (*n* = 56)	Research group (*n* = 59)	χ^2 value	*P* value
Cesarean section	28 (50.00)	4 (6.78)	26.723	< 0.001
Natural delivery	24 (42.86)	53 (89.83)	28.653	< 0.001
Forceps-assisted delivery	4 (7.14)	2 (3.39)	0.818	0.366

Table 3 Maternal and fetal outcomes of both groups, *n* (%)

Categories	Control group (*n* = 56)	Research group (*n* = 59)	χ^2 value	*P* value
Uterine inertia	17 (30.36)	7 (11.86)	5.950	0.015
Postpartum hemorrhage	6 (10.71)	1 (1.69)	4.089	0.043
Placental abruption	5 (8.93)	0 (0.00)	5.507	0.019
Neonatal lung injury	6 (10.71)	1 (1.69)	4.089	0.043
Neonatal asphyxia	4 (7.14)	0 (0.00)	4.366	0.037

Table 4 Patient satisfaction with nursing in both groups, *n* (%)

Categories	Control group (*n* = 56)	Research group (*n* = 59)	χ^2 value	*P* value
Satisfactory	17 (30.36)	36 (61.02)	-	-
Basically satisfactory	29 (51.79)	21 (35.59)	-	-
Unsatisfactory	10 (17.86)	2 (3.39)	-	-
Satisfaction	46 (82.14)	57 (96.61)	6.434	0.011

postpartum care for primiparas to improve their delivery experience, thus enhancing care quality and nursing satisfaction.

CONCLUSION

For primiparas, the nursing model of midwifery and postural and psychological interventions effectively improves maternal and fetal outcomes. Consequently, maternal anxiety and depression are alleviated, the natural delivery rate and nursing satisfaction increased, and the progress of labor is promoted. Therefore, this technique deserves clinical promotion.

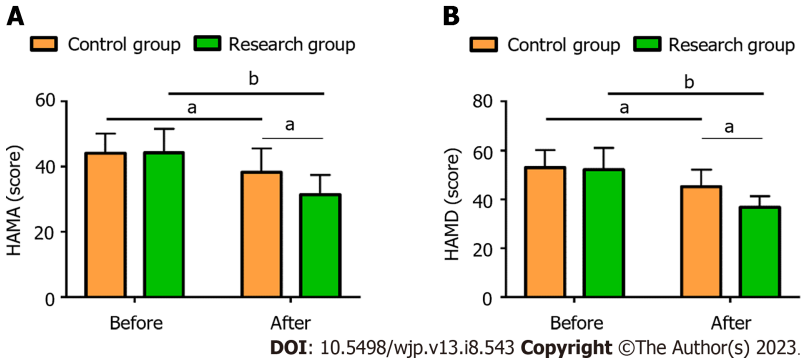

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Figure 1 Hamilton anxiety/depression-rating scale scores. A: Hamilton anxiety before and after intervention; B: Hamilton depression before and after intervention. [a]*P* < 0.05, [b]*P* < 0.01. HAMA: Hamilton anxiety; HAMD: Hamilton depression.

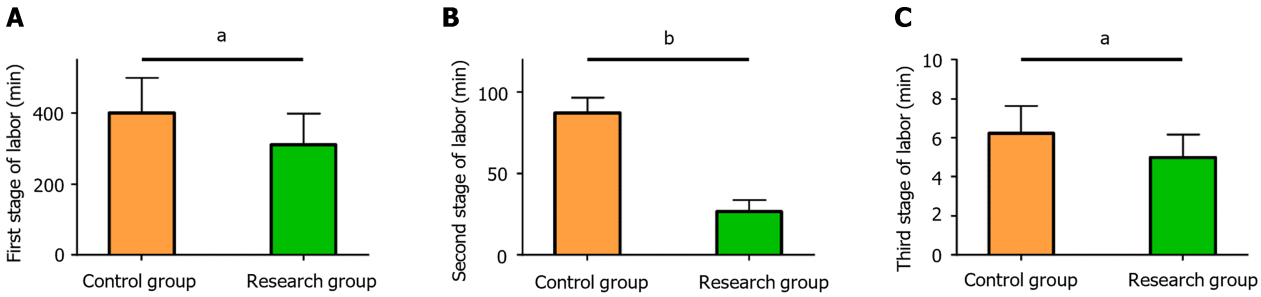

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Figure 2 Duration of each stage of labor. A: Duration of the first stage of labor in both groups; B: Duration of the second stage of labor in both groups; C: Duration of the third stage of labor in both groups. [a]*P* < 0.05, [b]*P* < 0.01.

ARTICLE HIGHLIGHTS

Research background

Parturients are physically and psychologically burdened during the perinatal period, so both primiparas and multiparas are at higher risk of depression. In addition, the mode of delivery of primiparas has an impact on maternal and infant outcomes, and those given birth by cesarean section (CS) are at a higher risk of complications.

Research motivation

To increase people's awareness of perinatal maternal management and provide reference for clinical care optimization of parturients during the perinatal period.

Research objectives

This study aims to analyze the effects of midwifery responsibility nursing plus postural interventions on maternal and fetal outcomes and negative emotions (NEs) of primiparas.

Research methods

In this study, 59 primiparas in the research group were treated by midwifery responsibility nursing plus posture interventions, and 56 primiparas in the control group were given conventional midwifery and routine nursing. The two groups were comparatively analyzed in terms of the mode of delivery, maternal and infant outcomes, NEs (Hamilton Anxiety/Depression-rating Scale, HAMA/HAMD), duration of labor, and nursing satisfaction.

Research results

Significantly higher natural delivery rate and nursing satisfaction, as well markedly lower CS and forceps delivery rates were determined in the research group compared with the control group; the research group also showed obviously lower incidence of uterine inertia, postpartum hemorrhage, placental abruption, neonatal lung injury, neonatal asphyxia and other events and shorter duration of each stage of labor than the control group; moreover, the HAMA and HAMD scores of the research group after intervention were significantly lower than those before treatment and in the control group.

Research conclusions

Midwifery responsibility nursing plus postural interventions is beneficial to improve maternal and infant outcomes, relieve maternal NEs, increase the rate of spontaneous labor, and shorten the duration of natural labor.

Research perspectives

This study mainly analyzes the application value of midwifery responsibility nursing plus postural intervention program in the care management of primiparas, focusing on the exploration and analysis of maternal and infant outcomes and NEs, in an attempt to provide an effective clinical basis for the care management of primiparas and contribute to improving their childbirth experience.

FOOTNOTES

Author contributions: Gao P contributed to the study conception and design, drafting manuscript, data analysis and interpretation; Gao P, Zhuang HP and Guo CQ contributed to the study conception, critical revision of article for important intellectual content; Gao P and Chen MY contributed to the study conception and design, critical revision of article for important intellectual content.

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ORIGINAL ARTICLE

Clinical Trials Study

Randomized control trial of a culturally adapted behavioral activation therapy for Muslim patients with depression in Pakistan

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Abstract

BACKGROUND

Behavioral activation therapy (BA) is as effective as cognitive behavior therapy (CBT) in treating depression and can be delivered by practitioners with much less psychological training, making it particularly suitable for low resource settings. BA that is culturally adapted for Muslims (BA-M) is a culturally adapted form of BA that has been found acceptable and feasible for Muslims with depression in the United Kingdom and Turkey; however, this is the first time that its efficacy has been determined through a definitive randomized controlled trial.

AIM

To compare the effectiveness of BA-M with CBT for Muslim patients with depression in Pakistan.

METHODS

One hundred and eight patients were randomized 1:1 to treatment arms in a parallel-group randomized controlled trial in hospital or community sites in Lahore, Pakistan. Recruitment followed self-referral or referrals from clinicians, consultants or relevant professionals at each site. Four measures were recorded by blinded assessors: The patient health questionnaire-9 (PHQ-9); the BA for depression scale short form (BADS-SF); symptom checklist-revised and the World Health Organization Quality-of-Life Brief Scale. All measures were recorded at baseline and post treatment; PHQ-9 and BADS-SF were also recorded at each session and at three month follow up. The primary analysis was to regress the PHQ-9 score after therapy upon the PHQ-9 score before therapy (baseline) and the type of therapy given, that is, analysis of covariance. In addition, analysis using PHQ-9 scores collected at each therapy session was employed in a 2-level regression model.

RESULTS
Patients in the BA-M arm experienced greater improvement in PHQ-9 score of 1.95 units compared to the CBT arm after adjusting for baseline values (P = 0.006) The key reason behind this improvement was that patients were retained in therapy longer under BA-M, in which patients were retained for an average 0.75 sessions more than CBT patients (P = 0.013). Patients also showed significant differences on physical (P < 0.001), psychological (P = 0.004) and social (P = 0.047) domains of Quality of Life (QoL) at post treatment level, indicating an increased QoL in the BA-M group as compared to the treatment as usual group. Some baseline differences were noted in both groups for BA scores and two domains of QoL scale: Physical and environment, which might have influenced the results, though the BA-M group showed more improvement at completion of therapy.

CONCLUSION
Results proved the efficacy of BA-M in reducing symptoms for depressed patients in Pakistan, indicating BA-M is a promising treatment modality for depression in future, particularly in low resource settings.

Key Words: Culturally adapted therapy; Behavioral activation; Depression; Pakistan; Muslim; Randomized control trial

Core Tip: Behavioral activation therapy that is culturally adapted for Muslims (BA-M) is a more effective treatment for depression in comparison to cognitive behavior therapy (CBT) for Muslim populations within the Pakistani cultural context. Increased engagement with the therapy appears to be the key reason for the significantly lower depression scores of patients receiving BA-M. As this treatment can be delivered by practitioners with much less psychological training than CBT, it is particularly suitable for Muslim patients in low resource settings.

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INTRODUCTION

Depression is a mood disorder with widespread occurrence throughout the world[1,2], affecting more than 300 million people around the globe according to World Health Organization (WHO) estimates. It is ranked as the largest cause of disability worldwide, with more than 4% global prevalence and an upward trend in developing countries, with almost half of cases occurring in South-East Asia[3]. In Pakistan, the risk of developing depression is 10%-25% higher for women than for men and this can be further increased by infertility[4], having a disabled child, emotional setbacks or family issues and disputes[5]. Depression can have a strong impact on family members as well as on the individual with depression[6]. Recorded rates of prevalence for maternal depression in Pakistan are among the highest globally at 28%–36%[7,8] and children of depressed mothers in this context are at an increased risk of being underweight, having poor health with more frequent episodes of diarrhea compared to the children of non-depressed mothers[8,9]. A strong relationship between infertility and psychological comorbidities has also been found[10] and evidence suggests that poverty is strongly linked with depression with almost 50% of low income mothers likely to be depressed[11]. This evidence highlights the need for a cost-effective treatment for depression in Pakistan. Interventions are needed to increase access to treatment and reduce the personal as well as social costs of depression, including impact on daily life, upbringing of children and loss in productivity, such as time taken off from work[12].

Despite the availability of a number of evidence-based therapies for depression, such as cognitive behavioral therapy (CBT), behavioral activation (BA), acceptance and commitment therapy (ACT) and exposure-based therapy[13-15], there is a growing body of empirical evidence about the need for, and effectiveness of, culturally adapted and religion-sensitive therapies[16]. Literature in this area shows that interventions that focus on culture and faith can effectively reduce depression and improve quality of life (QoL)[17,18]. Sensitivity to religious beliefs as a resource for health has been integrated into therapies such as CBT[17,19,20]; counseling[21,22]; ACT[23]; and trauma related therapies[24]. Integrating religious coping in adapted versions of such therapies has proved as effective as existing treatments and faith-adapted therapies have shown more positive results in the management of depressive symptoms in Muslim clients[25,26].

BA that is culturally adapted for Muslims (BA-M), developed for United Kingdom-based Muslim communities, is a successful faith-sensitive adaptation of an existing psychological treatment[27,28]. BA-M therapy is based on BA, an existing evidence-based psychosocial treatment for depression that focuses on clients' values and links these with behavioral goals[29-31]. Piloting of this adapted version has shown that BA-M was feasible within a United Kingdom healthcare setting and was very positively received by Muslim clients[28]. The inclusion of 'client values' in therapy makes BA a particularly suitable treatment for adaptation to diverse cultural needs and it has been successfully adapted and tailored to multiple cultural contexts across the globe[32-34]. The present research is the first study globally to assess

the efficacy of BA-M through a randomized controlled trial with adult depressed patients. The trial was conducted in Pakistan, a low income setting in which the approach was considered relevant for the majority of the population.

MATERIALS AND METHODS

A three-center two-arm parallel block-randomized controlled trial was conducted to estimate the effectiveness of BA-M to treat depression in Pakistan compared to treatment as usual (TAU) using a 1:1 allocation ratio. Patients were allocated at each center in blocks of two with one being randomized to TAU and the other allocated to treatment by BA-M (BA culturally adapted to Muslim faith). There were no changes to the recruitment procedure or methods during the trial. The trial was registered with ISRCTN. Ethical approval was granted by the Faculty of Medicine and Health Ethics Committee at the University of Leeds and the National Bioethics Committee, Pakistan.

Participants

Patients with depression were recruited from outpatient departments of three targeted data sites in Lahore, Pakistan: Mayo Hospital (Mayo), Punjab Institute of Mental Health (PIMH) and the Centre for Clinical Psychology, University of the Punjab, Lahore (CCP). Recruitment followed self-referral or referrals from clinicians, consultants or relevant professionals at each site. All patients were over 18 years of age.

Assessment measures

An Urdu version of the patient health questionnaire (PHQ-9) was used to screen for depression[35] alongside the symptom checklist-revised (SCL-R) - an indigenous screening tool for which psychometric properties are well established [36]. Patients were invited to take part in the trial if their depression score on PHQ-9 was at least 10 and if they had no comorbid psychological disorders, such as bipolar disorder or schizophrenia, could understand the study measures and could give informed consent.

Intervention

Patients were randomized to receive either TAU, which was CBT at each site, or BA, adapted to meet the needs of Muslims patients (BA-M). TAU comprised of 8 sessions of CBT.

BA-M is a culturally tailored version of BA, an existing evidence-based psychosocial treatment for depression, which is as effective as CBT but requires less practitioner training[37]. BA-M comprises 6–12 sessions of treatment involving a values assessment. Muslim clients who select religion as a personal value during this assessment are offered the choice of using a self-help booklet designed to help their recovery[27]. The booklet draws on Islamic religious teachings to promote therapeutic goals and 'positive religious coping' that supports resilience, hopefulness and self-esteem[38]. Patients were treated in outpatient clinics at the three sites following referrals to clinical psychologists involved in delivering the intervention for the trial.

Outcomes

A demographic information sheet with details of age, gender, education, birth order, family income and type, psychological illness, physical illness, current diagnosis and history of treatment related to psychological issues was administered to each recruited patient. The primary outcome, on which the trial was powered, was the change in PHQ-9 score following therapy, that is, the difference between the PHQ-9 score after therapy and that recorded before therapy commenced. The PHQ-9 measure was used to assess depression and determined the extent to which patients had experienced depressive symptoms over the previous two weeks. The nine items were rated on a 0-3 scale ranging from 'not at all' to 'nearly every day'. The PHQ-9 has adequate construct validity and sensitivity to change[39]. In the present study, the Urdu translated version of PHQ-9 was used[7].

There were several secondary outcomes collected to provide greater understanding of the performance of BA-M as a therapy. PHQ-9 was collected not just at baseline and at the end of treatment but at the start of every therapy session. Two other measures were collected before and after therapy. The 9-item BA for depression scale short form (BADS-SF) was used to track activation, including when and how clients became activated during the course of treatment. This measure was developed to improve the original BADS measure and has stronger psychometric properties[40]. The SCL-R [36] is an indigenous checklist which assesses six psychopathologies: Depression, anxiety, obsessive compulsive disorder, somatization, schizophrenia and low frustration tolerance. In the present study, the subscale of depression with 24 items was used to assess the degree of depression in depressed patients. The items are rated on a 4-point Likert scale and psychometric properties are well established for all subscales of SCL-R. A fourth measure, the WHO QoL Brief Scale (WHOQOL-BREF)[41], developed by the WHO with 26 items, was used to assess QoL in depressed patients. This covers 4 major domains: physical health, psychological health, social relationships and environment. One item from each of the 24 facets contained in the WHOQOL-100 was included along with two items from the overall QoL and the general health facets. A further outcome measure was the number of sessions attended by each patient to assess patient engagement with therapy.

Sample size

Power calculations for the sample were based on change in PHQ-9 from baseline (PHQ-9-0) to 3 mo after therapy (PHQ-9-3). Drawing on earlier research, we anticipated that PHQ-9 would have a standard deviation of 5 units and that the

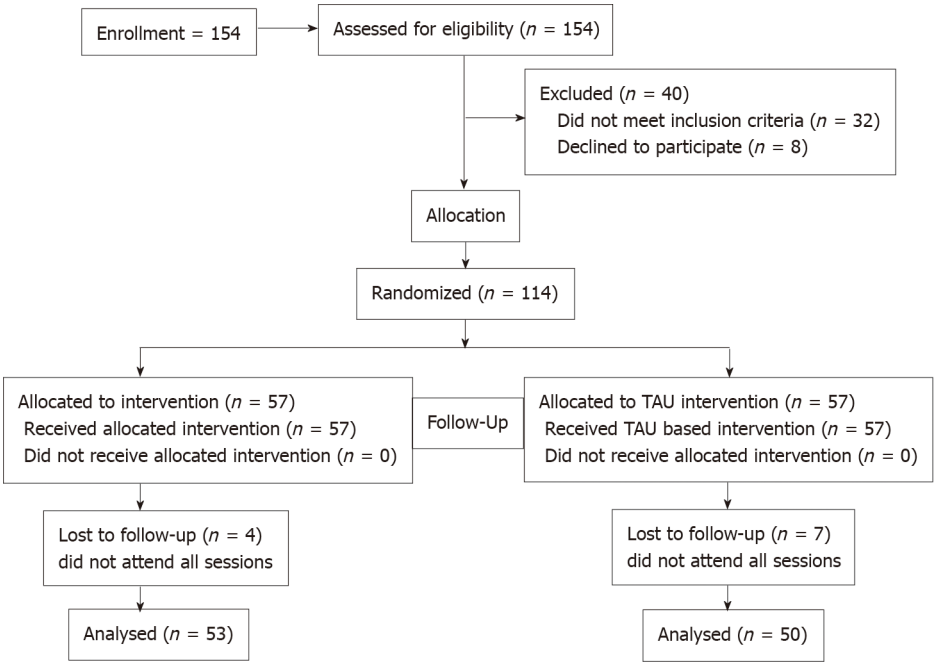

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Figure 1 Flow diagram representing process of the study. TAU: Treatment as usual.

correlation between before and after measurements would be 0.75. Consequently, we anticipated that the difference between PHQ-9-3 and PHQ-9-0 would have a standard deviation of 3.54 units[42]. A minimal clinically important difference in PHQ scores was considered to be 2 units on PHQ-9. Using a two-sample *t*-test to assess the difference between the groups, with 5% significance level, the number required to achieve 80% power is 50 patients per group. It was anticipated that around 15% patients would drop out of the trial before the completion of therapy. Adjusting for drop out thus yielded a sample size of 59 patients per group.

Randomization

At each site, patients were recruited in pairs by a blind assessor who screened for depression and assigned individuals from each pair at random (using a Microsoft Excel random number generator value below 0.5) to TAU or BA-M. This ensured a random sample balanced for each site and for therapy. It was not possible to conceal the randomization from either the patient or those delivering therapy.

Statistical methods

The primary analysis was to regress the PHQ-9 score after therapy upon the PHQ-9 score before therapy (baseline) and the type of therapy given. This analysis of covariance approach was considered to be the optimum statistical method for the analysis of continuous outcomes of randomized control trials (RCTs) where baseline measurements are available[43].

Analysis was undertaken on a complete case basis and the implication for bias due to drop out was considered through analysis of the secondary outcomes. It was not appropriate to assume that data was missing at random since patients may have withdrawn from the trial or from therapy because they were either dissatisfied with their progress through therapy or improved so much that they considered that therapy was no longer required. Hence imputation methods which are valid under the assumption of missing at random were not appropriate here.

As a secondary analysis of PHQ-9, all of the measurements made were considered in a two- level regression analysis with measurements nested within patients by the inclusion of a random intercept for patient. This provided the average change in score per session for each of the two therapies. A Wald test for the interaction term made it possible to formally test if there was a difference in therapy per session.

The average number of sessions attended for each arm was compared with a two-sample *t*-test to explore the duration of the therapy in each arm. Other secondary outcomes, namely BADS-SF, the total SCL-R score, and the four domains of WHOQOL-BREF were compared with analysis of covariance, as for the primary analysis of PHQ-9.

RESULTS

Participant flow

For each group, TAU and BA-M, the numbers of participants who were randomly assigned, received intended treatment and were analyzed for the primary outcome, namely change in PHQ-9 after treatment, is shown in Figure 1.

Table 1 Baseline characteristics of patients stratified by therapy arm

Characteristics		BA-M		TAU		*P* value
		Mean or count	SD or %	Mean or count	SD or %	
Age		32.3	9.6	33.8	11.5	0.437
Gender	Men	17	30%	24	42%	0.242
	Women	40	70%	33	58%	
Data site	CCP	18	34%	22	39%	0.880
	PIMH	21	40%	21	37%	
	Mayo	14	26%	14	25%	
Education	Below primary	6	11%	6	11%	0.300
	Matric	11	20%	14	25%	
	FA/A Level	9	16%	12	21%	
	Other	24	43%	14	25%	
	Middle/secondary	6	11%	11	19%	
Marital status	Married	27	47%	19	33%	0.039
	Sep/divorced/widowed	5	9%	15	26%	
	Unmarried	25	44%	23	40%	
Family system	Nuclear	32	56%	31	54%	0.999
	Joint	25	44%	26	46%	
Working status	Yes	25	45%	21	37%	0.514
	No	31	55%	36	63%	
SES	Lower class	14	25%	21	37%	0.247
	Middle or upper class	42	75%	36	63%	
PHQ (Pre)		19.5	4.9	20.1	4.1	0.487
BADS (Pre)		20.2	8.4	15.6	6.3	0.001
SCL-R (Dep)		41.9	9.9	43.1	8.2	0.506
D1 (Pre)	Physical health	17.9	4.9	14.7	4.8	0.001
D2 (Pre)	Psychological health	12.3	3.3	11.7	3.3	0.333
D3 (Pre)	Social relationships	8.4	2.6	7.9	2.6	0.298
D4 (Pre)	Environment	22.4	5.2	20.0	5.1	0.014

BA-M: Behavioral activation therapy that is culturally adapted for Muslims; TAU: Treatment as usual; CCP: Centre for Clinical Psychology, Lahore; PIMH: Punjab Institute of Mental Health, Lahore; FA/A: Upper secondary level education; PHQ: Patient health questionnaire; BADS: Behavioral activation for depression scale short form; SCL-R: Symptom checklist-revised; D: Domain; Dep: Depression.

Recruitment

The first patient was recruited in March 2020 and recruitment continued until at least 59 patients completed their therapy in each arm. Recruitment was then closed in August 2021, having established that at least 50 patients had been recruited and retained until the end of therapy.

Baseline data

Characteristics between the two groups were similar (Table 1) apart from the initial BADS-SF score and the initial values of the D2 (psychological health) and D4 (environment) domains of WHOQOL-BREF. Analysis methods were designed to adjust for these baseline imbalances.

Drop out

Seven of 57 patients assigned to TAU and 4 of 57 patients assigned to BA-M withdrew from the trial. Data after baseline collection was not available for analysis for these patients. Table 2 shows the characteristics of patients who were lost to follow up compared to those who were retained.

Table 2 Characteristics of lost and retained patients

Characteristics		Lost to follow up (*n* = 11)	Retained (*n* = 103)	*P* value
Age, mean (SD)		35.27 (13.94)	32.83 (10.19)	0.469
Gender	Men	9 (82%)	32 (31%)	0.003
	Women	2 (18%)	71 (69%)	
Education	Below primary	1 (10%)	11 (11%)	
	Matric	3 (30%)	22 (21%)	
	FA/A Level	1 (10%)	20 (19%)	0.915
	Other	3 (30%)	35 (34%)	
	Middle/secondary	2 (20%)	15 (15%)	
Marital status	Married	3 (27%)	43 (42%)	0.617
	Sep/divorced/widowed	2 (18%)	18 (18%)	
	Unmarried	6 (55%)	42 (41%)	
Family system	Nuclear	10 (91%)	53 (52%)	0.029
	Joint	1 (9%)	50 (49%)	
Working status	Yes	5 (46%)	41 (40%)	0.989
	No	6 (55%)	61 (60%)	
SES	Lower class	6 (55%)	29 (28%)	0.151
	Middle or upper class	5 (46%)	73 (72%)	
PHQ Pre		20.18 (2.82)	19.79 (4.71)	0.786
BADS Pre		14.09 (4.11)	18.34 (7.90)	0.082
SCL-R (Dep)		36.91 (9.61)	43.14 (8.88)	0.030
D1 (Pre)	Physical health	16.64 (2.94)	16.33 (5.26)	0.850
D2 (Pre)	Psychological health	12.18 (3.06)	11.94 (3.31)	0.818
D3 (Pre)	Social relationships	8.00 (1.41)	8.17 (2.70)	0.842
D4 (Pre)	Environment	20.18 (3.06)	21.31 (5.44)	0.501

SES: Socioeconomic status; FA/A: Upper secondary level education; PHQ: Patient health questionnaire; BADS: Behavioral activation for depression scale short form; SCL-R: Symptom checklist-revised; D: Domain; Dep: Depression

Male patients and those in nuclear families were seen to be more susceptible to drop out. Feedback from therapists indicated that therapy sessions during working hours were more likely to adversely affect attendance by men and the average baseline SCL-R value was also lower among drop outs, indicating less severe depressive symptoms in this group. Data for 50 TAU patients and 53 BA-M patients was available for analysis.

Outcomes and estimation

A summary of the outcome variables after therapy is provided in Table 3. This provides unadjusted *t*-test comparisons of the outcomes between groups. Significant post treatment differences in depression ($P = 0.006$) and QoL scores were found in the BA group compared to TAU following completion of treatment.

The primary outcome (PHQ-9) was also regressed upon baseline values and therapy arm and the table of regression coefficients is given in Table 4.

From the coefficients in Table 4, it is seen that generally those in the TAU arm have higher PHQ-9 scores after therapy and that an adjustment for baseline values of PHQ-9 is important since the coefficient is statistically significant at the 5% level. Plots of residuals (not shown due to space limitations) were seen as satisfactory. The interpretation for this trial based on the primary analysis is that BA-M is associated with a greater reduction in depression symptoms as measured by PHQ-9 after completion of therapy.

Further analyses

The analysis of secondary outcomes BADS-SF and SCL-R are summarized in Table 5.

Table 3 Summary of outcome after therapy

Characteristics	BA-M	TAU	*P* value
n	57	57	
Drop Out	4 (7%)	7 (12%)	0.526
Retained	53 (93%)	50 (88%)	
PHQ (Post), mean (SD)	4.19 (3.42)	6.18 (3.85)	0.006
BADS (Post)	34.34 (7.32)	27.90 (8.53)	< 0.001
SCL-R (Dep)	16.00 (8.08)	19.96 (7.74)	0.013
D1 Physical Health (Post)	25.85 (2.91)	22.84 (3.35)	< 0.001
D2 Psychological Health (Post)	19.74 (3.08)	17.88 (3.26)	0.004
D3 Social Relationships (Post)	10.45 (1.96)	9.64 (2.15)	0.047
D4 Environment (Post)	27.83 (4.91)	26.48 (4.44)	0.147
Number of Sessions	9.00 (1.77)	8.25 (1.39)	0.013

BA: Behavioral activation therapy; BA-M: Behavioral activation therapy that is culturally adapted for Muslims; TAU: Treatment as usual; PHQ: Patient health questionnaire; BADS: Behavioral activation for depression scale short form; SCL-R: Symptom checklist-revised; D: Domain; Dep: Depression.

Table 4 Coefficients for the regression of the patient health questionnaire-9 post-therapy measurement on baseline and therapy arm

Characteristics	Estimate	95%CI	*P* value
Intercept	1.205	(-1.887, 4.298)	0.441
TAU Arm	1.946	(0.545, 3.347)	0.007
Baseline PHQ	0.152	(0.002, 0.301)	0.046

TAU: Treatment as usual; PHQ: Patient health questionnaire.

As the PHQ-9 tool was used at every therapy session, more detailed longitudinal data was available. Values are plotted in Figure 2.

Figure 2 shows that the PHQ-9 trajectories might be simply modeled with a linear decrease by session. This was undertaken with a linear mixed effects model with a random intercept for patient. The coefficients are shown in Table 6.

The results revealed that the interpretation of the coefficients in Table 6 showed a decline in PHQ-9 of 2.26 points on average for every session attended and there is little evidence of BA-M being superior to TAU on this basis. The reason behind the statistically significant improvement due to BA-M therapy rather than TAU, as seen in the analysis of primary outcome, is that patients under BA-M are retained in therapy longer. Table 3 also shows that the mean number of sessions attended increases from 8.25 under TAU to 9.00 under BA-M ($P = 0.013$).

DISCUSSION

This is the first trial evaluation of the BA-M culturally adapted therapy for depression globally. Previous evaluations have shown feasibility and acceptability to therapists and patients in both United Kingdom[27] and Turkish settings[44]. Findings confirm the importance of culturally adapted approaches when delivering mental health therapies developed in Western contexts to non-Western populations[16] and the benefits of faith-sensitive approaches in general[25]. The results of the current study support the efficacy of BA-M therapy in line with the wider literature on BA as a cost-effective and efficacious alternative to CBT[45]. Patients in the BA-M group showed lower levels of depression (PHQ-9 and SCL-R) and higher scores of BA (BADS-SF) post treatment, indicating the effectiveness of BA-M therapy in reducing depression and increasing helpful activity in patients. Patients also showed significant differences on physical ($P < 0.001$), psychological ($P = 0.004$) and social ($P = 0.047$) domains of QoL at post treatment level, indicating an increased QoL in the BA-M group as compared to the TAU group.

Retention in BA-M therapy

Fewer patients dropped out of the BA-M group than from the TAU group and this was seen to lead to greater benefit since the improvement in symptoms per session was consistent throughout the usual therapy period of 8 wk. Patients who dropped out tended to have low scores on the depression scale as compared to those who were retained. The results

Table 5 Coefficients from the regression for secondary outcomes from analysis of covariance models

Characteristics	Estimate	95%CI	*P* value
BADS			
Intercept	36.332	(31.629, 41.035)	< 0.001
Arm TAU	-6.854	(-10.076, -3.631)	< 0.001
Baseline BADS	-0.098	(-0.302, 0.107)	0.346
SCL-R (Dep)			
Intercept	0.455	(-6.723, 7.633)	0.900
Arm TAU	3.802	(0.960, 6.644)	0.009
Baseline SCL-R (Dep)	-0.098	(-0.302, 0.107)	0.346
WHOQOL (D1: Physical)			
Intercept	22.948	(20.662, 25.235)	< 0.001
Arm TAU	-2.489	(-3.737, -1.241)	< 0.001
Baseline (D1: Physical)	0.162	(0.043, 0.281)	0.008
WHOQOL (D2: Psychological)			
Intercept	16.097	(13.71, 25.235)	< 0.001
Arm TAU	-1.614	(-2.809, -0.420)	0.009
Baseline (D2: Psychological)	0.295	(0.133, 0.476)	0.002
WHOQOL (D3: Social)			
Intercept	7.836	(6.583, 9.089)	< 0.001
Arm TAU	-0.688	(-1.424, 0.048)	0.066
Baseline (D3: Social)	0.313	(0.176, 0.450)	< 0.001
WHOQOL (D4: Environment)			
Intercept	18.072	(14.496, 21.648)	< 0.001
Arm TAU	-0.328	(-1.967, 1.312)	0.693
Baseline (D4: Environment)	0.435	(0.283, 0.586)	< 0.001

BADS: Behavioral activation for depression scale short form; SCL-R: Symptom checklist-revised; WHOQOL: World Health Organization quality of life; D: Domain; Dep: Depression; TAU: Treatment as usual; PHQ: Patient health questionnaire.

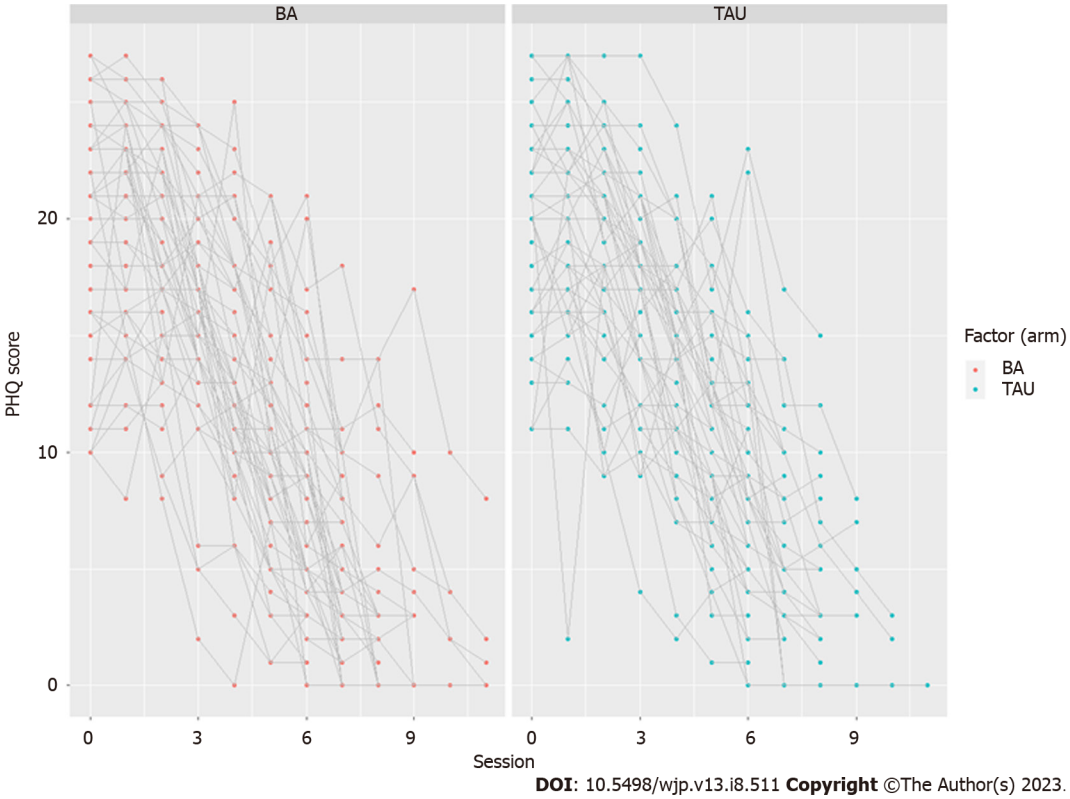
Table 6 Coefficients for the fixed effects of the longitudinal model for patient health questionnaire-9

Characteristics	Estimate	95%CI	*P* value
Overall Intercept	21.536	(20.549, 22.524)	< 0.001
TAU Arm	0.396	(-1.010, 1.800)	0.582
Session	-2.260	(-2.363, -2.156)	< 0.001
TAU-session interaction	0.10203	(-0.058, 0.261)	0.210

TAU: Treatment as usual.

also showed that men and those who were living in nuclear families were found to be more susceptible to drop out.

The particular benefits of BA-M appear to have been achieved as a result of patient retention in therapy and this is an important factor in recovery from depression. As in the United Kingdom study for BA-M[27], the faith-sensitive approach appears to have a motivating influence on patients. Qualitative findings from the United Kingdom study indicated that most patients were enthusiastic about and motivated by the engagement with religious identity in this approach. This was designed to support 'positive religious coping' that increased resilience, hope and self-esteem[38]. The findings confirm previous research, both on value-based practice that takes account of cultural context and on BA, which partic-



DOI: 10.5498/wjp.v13.i8.511 **Copyright** ©The Author(s) 2023.

Figure 2 Plot of patient health questionnaire-9 values observed at every therapy session. BA: Behavioral activation therapy; TAU: Treatment as usual; PHQ: Patient health questionnaire.

ularly focuses on increasing activities that are linked to an individual's values and reward systems, consequently enhancing their behavioral patterns and reducing depressive symptoms[46,47].

We note there were important baseline differences in both groups for BA scores and two domains of QoL scale: Physical and Environment. The BA-M group showed more BA and QoL related to physical health and environment as compared to the TAU group. These may have influenced findings although it is clear that there was greater improvement in physical, psychological and social QoL domains for the BA-M group at completion of treatment.

There were also gender differences in retained and dropped out patients as 82% of dropped out patients were men. Differences in the family system of patients were also apparent as 91% of dropped out patients were from nuclear families.

CONCLUSION

In conclusion, this RCT demonstrated the benefit of BA-M, a culturally adapted form of BA, over usual treatment (CBT) at the end of therapy. It is clear that both CBT and BA-M are successful therapies for reducing depression, however, findings suggest that the additional benefit of BA-M is due to greater retention of participants in therapy that is likely to be due to the cultural adaptation. The trial confirms existing evidence on the benefits of therapy that supports activation of religious behaviors as a resource for health and fulfills the need for rigorous research in a population sample that has hitherto been underrepresented and for whom such behaviors may be critical to treatment outcomes[48].

ARTICLE HIGHLIGHTS

Research background

Depression is the largest cause of disability worldwide and can strongly impact on families and society as well as individuals. Culturally appropriate, accessible and cost-effective treatments are needed in low resource settings such as Pakistan. This study is the first randomized control trial globally of behavioral activation (BA) therapy that is culturally adapted for Muslim patients (BA-M).

Research motivation

The main focus was to explore whether BA-M, as a culturally adapted therapy, would achieve better results than

cognitive behavior therapy (CBT), a standard treatment developed in a Western context. BA can be delivered by practitioners with much less psychological training than CBT, making it particularly suitable for low resource settings. This research has great significance for future studies on how to reduce depression and increase access to treatment for Muslim communities worldwide.

Research objectives

The purpose of the study was to compare the effectiveness of BA-M with CBT for Muslim patients in Pakistan.

Research methods

Clinical data were analyzed for 108 patients in a parallel-group randomized controlled trial in hospital or community sites in Lahore, Pakistan. Four measures were recorded by blinded assessors: The patient health questionnaire-9 (PHQ-9); the BA for depression scale short form (BADS-SF); symptom checklist-revised and the WHOQOL-BREF quality of life (QoL) scale. All measures were recorded at baseline and post treatment; PHQ-9 and BADS-SF were also recorded at each session and at three month follow up. The primary analysis was to regress the PHQ-9 score after therapy upon the PHQ-9 score before therapy (baseline) and the type of therapy given. In addition, analysis using PHQ-9 scores collected at each therapy session was employed in a 2-level regression model.

Research results

Patients in the BA-M arm experienced greater improvement in PHQ-9 score compared to the CBT arm and were retained in therapy longer than those receiving CBT after adjusting for baseline values. BA-M patients also showed significant differences on physical, psychological and social domains of QoL at post treatment level, indicating an increased QoL in the BA-M group as compared to the CBT group.

Research conclusions

BA-M is a culturally appropriate treatment for depression that achieves better results than CBT, which is current standard treatment in Pakistan. BA-M can be delivered by practitioners with much less psychological training than CBT and is a promising treatment modality for depression in Muslim communities, particularly in low resource settings.

Research perspectives

Future research should evaluate acceptability and effectiveness of BA-M in other Muslim populations, including where these constitute minorities, and issues related to implementation and scale-up.

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FOOTNOTES

Author contributions: Dawood S was involved in design of the study, led the data collection and conduct of research on data sites, contributed to analysis and drafted the write-up of results; West RM contributed to the trial design, led statistical analysis and contributed to the writing-up of results and final paper; Mir G developed the concept for the study, contributed to the methodology of the randomized control trial and writing of the final paper and gave final approval of the version to be published; All authors contributed and approved the final manuscript.

Institutional review board statement: This study has been reviewed and approved by the School of Medicine Research and Ethics Committee at the University of Leeds, United Kingdom, No. MERC-19-034; and the National Bioethics Committee, Pakistan, No. NBC-459/20/726.

Clinical trial registration statement: This study is registered at ISRCTN, No. 35418604.

Informed consent statement: All study participants provided informed written consent prior to their inclusion in the current study.

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

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ORIGINAL ARTICLE

Observational Study

Effects of sports on school adaptability, resilience and cell phone addiction tendency of high school students

Li-Qiang Zhang, Hui-Na Gao

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Abstract

BACKGROUND

Sport help promote healthy physical and mental development of high school students. To date, there have been few studies on the effect of sport on school adaptability, resilience and cell phone addiction tendency of high school students.

AIM

To explore the effects of sports on school adaptability, resilience and cell phone addiction of high school students.

METHODS

A stratified random sampling method was used to select 600 students from two high schools in Lhasa, and Physical Activity Rating Scale, School Adjustment Scale for High School Students, Chinese Adolescents Resilience Scale, and Mobile Phone Addiction Index were used for field questionnaire survey.

RESULTS

Sport was positively correlated with school adaptability and resilience ($P < 0.01$), school adaptability was positively correlated with resilience ($P < 0.01$) and cell phone addiction was negatively correlated with sports, school adaptability and resilience ($P < 0.01$). The direct effect of sport on cell phone addiction was significant ($P < 0.001$), accounting for 20.51% of the total effect. The mediating effect of school adaptability on sport and cell phone addiction was significant ($P < 0.001$), accounting for 17.38% and 35.36% of the total effect value, respectively. School adjustment and resilience had a significant chain-mediated effect on sport and cell phone addiction ($P < 0.001$), accounting for 26.75% of the total effect.

CONCLUSION
Sport affected the cell phone addiction tendency of senior high school students through the mediating effect of school adaptability and resilience, and through the chain mediation effect of both.

Key Words: Sport; High school students; School adaptability; Resilience; Cell phone addiction

Core Tip: Sport is beneficial to the development of heart and lung function and motor system, and can develop physical strength and promote mental health. This study analyzed the questionnaire data of 560 high school students' sporting activity, school adaptability, resilience and cell phone addiction tendency. By constructing a chain mediation model, the relationship between sport and school adaptability, resilience and cell phone addiction tendency was obtained, providing a theoretical basis for the physical and mental health development of high school students.

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INTRODUCTION

High school students are in a stage of growth and development, and sport plays a particularly important role in promoting their physical and mental health[1]. However, many high school students neglect sport because they study all day under academic pressure or are addicted to their cell phones[2,3]. The decline in sport could have a negative effect on physical and mental health of high school students[4]. Sport can improve high school students' adaptability to school, which can promote interpersonal relations and enthusiasm for learning[5]. Sport can enhance the resilience of high school students, and help them to face the pressure and difficulties brought by school life with a more positive and optimistic attitude[6]. Sport is also linked to lower levels of cell phone addiction among senior high school students[7]. Although many studies have shown that sport has an impact on school adaptability, resilience and cell phone addiction of adolescent students[8-11], few studies have combined sport with these other aspects in high school students. Therefore, by establishing the amount of sport of high school students, we analyzed the relationship between sport and senior high school students' school adaptability, resilience and cell phone addiction tendency. We also discussed the influence of sport on high school students' school adaptability, resilience and cell phone addiction tendency.

MATERIALS AND METHODS

Research object

From March to June 2022, a questionnaire survey was conducted among students from two high schools in Lhasa using stratified random sampling. A total of 600 students were selected according to different grades, and 200 in each grade were selected. The mean age was 16.56 years ± 1.01 years. There were 320 male students (53.33%) with an average age of 16.58 years ± 1.0 years. There were 280 female students (46.67%) with an average age of 16.53 years ± 1.04 years. We included senior grade one, two and three students, and students gave informed consent to complete the questionnaire. We excluded students with poor physical and mental health, and those who were unable to cooperate with the questionnaire. This study is in accordance with the Declaration of Helsinki.

Questionnaire

The questionnaire was conducted with the consent of the students, their parents and the school. Before the test, a mental health professional instructed the students to fill in the questionnaire according to their own situation. After filling in the questionnaire, it was recovered immediately. Six hundred questionnaires were sent out, and 560 (93.33%) were collected.

Research tools

Physical activity rating scale: The Physical Activity scale modified by Liang *et al*[12] was adopted, which measured sport from three dimensions of participation; namely time, intensity and frequency. Score = sport intensity score "(sport time score-1)" sport frequency score. Each dimension was divided into five grades, scoring 1-5 points. Scores ranged from 0 to 100: Low level of sport ≤ 19 points; level 20-42 points, and high level ≥ 43 points. Cronbach's α was 0.82.

School adjustment scale: We used Hou *et al*[13] School Adjustment Scale for Senior High School Students. The scale consisted of 82 items, including seven dimensions of academic adjustment, peer relationship, school attitude, class

activity adjustment, emotional adjustment, conflict in teacher-student relationship, and intimacy of teacher-student relationship. A 5-point Likert 5 scale was used. Scores ranged from 1 to 5. All dimensions were added together to obtain the School Adaptation Score. A higher total score indicated better school adaptability. Cronbach's α was 0.964.

Resilience scale for Chinese adolescents: Hu *et al*[14] compiled the Resilience Scale for Chinese adolescents. The scale consisted of 27 items, including five dimensions: Goal focus, positive cognition, emotional control, family support, and interpersonal assistance. The scale used a 5-point Likert scoring method. Scores ranged from 1 to 5, and a higher total score indicated greater resilience. Cronbach's α was 0.86.

Mobile phone addiction index: The Mobile Phone Addiction Index was compiled by Leung[15]. There were 17 items, including four dimensions: Loss of control, withdrawal, inefficiency and escape. A 5-point Likert scoring method was used. Scores ranged from 1 to 5, and a score < 34 was considered to show no cell phone addiction, 34-51 mild addiction, 52-68 addiction, and 68-85 severe addiction. Cronbach's α was 0.90.

Statistical analysis

SPSS 26.0 statistical software was used for data analysis. Descriptive statistics, *t* test, analysis of variance, and correlation analysis were conducted on the collected data, and PROCESS was used to test the mediating effect. The statistical significance was $P < 0.05$.

RESULTS

Essential features of senior high school sport

The total score for level of sport in high school students was 16 (6, 30) points (Table 1). The level of sport of high school students was mostly in the low sport level, accounting for 59.29% of the total number.

The level of sport among high school students was significantly higher in male than female students ($P < 0.05$) (Table 2). Sport intensity, time and frequency and total score were also significantly higher in male students ($P < 0.05$), indicating that male students had a greater need of sport.

There were no significant differences in sport intensity, time and frequency in senior grade one, two and three students ($P > 0.05$) (Figure 1).

Among the 560 high school students participating in the survey 332 (59.29%) had a low level of sport, 144 (25.71%) had a medium level, and 84 (15%) had a high level (Table 1). Among the 300 male students, 157 (52.33%) had a low level of sport, 82 (27.33%) had a medium level, and 61 (20.34%) had a high level. Among the 260 female students, 175 (67.31%) had a low level of sport, 62 (23.85%) had a medium level, and 23 (8.84%) had a high level. Among the 184 senior grade 1 high school students, 107 (58.15%) had a low level of sport, 53 (24.81%) had a medium level, and 24 (13.04%) had a high level. Among the 192 senior grade two students, 115 (59.90%) had a low level of sport, 46 (23.96%) had a medium level, and 31 (16.14%) had a high level. Among the 184 senior grade 3 students, 110 (59.78%) had a low level of sport, 45 (24.46%) had a medium level, and 29 (15.76%) had a high level.

Specific analysis of different levels of sports in senior high school sports

As shown in Tables 3-5, there was no significant difference in gender and grade among high school students of low, medium and high sports levels ($P > 0.05$), indicating that there was no gender and grade difference between high school students at the same sports level. Therefore, the following analysis was performed in three groups of high school students at low, medium and high sports levels to analyze resilience, school adaptability and cell phone addiction tendency.

Effect of level of sport on school adaptability of high school students

There were significant differences in the scores for academic adjustment, peer relationship, school attitude, class activity adjustment, emotional adjustment, conflict in teacher-student relationship, intimacy of teacher-student relationship when comparing low, medium and high levels of sport ($P < 0.05$) (Figure 2A). There were significant differences in the seven dimensions of school adaptability between students with low and medium levels of sport, low and high levels of sport, and medium and high levels of sport ($P < 0.05$).

Effect of level of sport on resilience of high school students

The total scores for goal focus, positive cognition, emotional control, family support, and interpersonal assistance were significantly different between students with low, medium and high levels of sport ($P < 0.05$) (Figure 2B). There were significant differences between these five dimensions when comparing students with low and medium levels of sport, low and high levels of sport, and medium and high levels of sport ($P < 0.05$).

Effect of level of sport on cell phone addiction tendency of high school students

There were significant differences in loss of control, withdrawal, escape, and inefficiency among students with low, medium and high levels of sport ($P < 0.05$) (Figure 2C). There were significant differences in these four dimensions of cell phone addiction tendency between students with low and medium levels of sport, low and high levels of sport, and medium and high levels of sport ($P < 0.05$).

Table 1 Analysis of characteristics of different levels of sport

	Low level (≤ 19 points)	Medium level (20-42 points)	High level (≥ 43 points)	Total
Score (point)				
Intensity	3 (2, 3)	3 (3, 4)	4 (3, 5)	3 (2, 4)
Time	2 (1, 3)	4.0 (3.0, 4.5)	5 (4, 5)	3 (2, 4)
Frequency	3 (2, 4)	3 (3, 4)	4 (4, 5)	3 (2, 4)
Total score	6.0 (0, 13.5)	27 (24, 34)	49 (48, 62)	16 (6, 30)
Gender, *n* (%)				
Male	157 (52.33)	82 (27.33)	61 (20.34)	300 (100.00)
Female	175 (67.31)	62 (23.85)	23 (8.84)	260 (100.00)
Total	332 (59.29)	144 (25.71)	84 (15.00)	560 (100.00)
Grade, *n* (%)				
Senior 1	107 (58.15)	53 (24.81)	24 (13.04)	184 (100.00)
Senior 2	115 (59.90)	46 (23.96)	31 (16.14)	192 (100.00)
Senior 3	110 (59.78)	45 (24.46)	29 (15.76)	184 (100.00)
Total	332 (56.29)	144 (25.71)	84 (15.00)	560 (100.00)

Table 2 Gender differences in sports of high school students

	Male (*n* = 300)	Female (*n* = 260)	*Z*	*P*
Intensity	3 (2, 4)	3 (2, 4)	3.522	< 0.001
Time	3 (2, 4)	3 (2, 4)	3.002	0.003
Frequency	3 (2, 4)	3 (2, 4)	2.438	0.015
Total score	18 (6, 36)	12 (4, 24)	3.520	< 0.001

Table 3 Effect of gender and grade in high school students with low level of sport

	Intensity	Time	Frequency	Total score
Male	3 (2, 4)	2 (1, 3)	3 (2, 4)	6 (0, 12)
Female	2 (2, 3)	2 (2, 3)	3 (2, 3)	6.0 (2.0, 13.5)
Z	1.709	0.656	1.107	0.323
P	0.087	0.512	0.268	0.747
Senior 1	3.0 (2.0, 3.5)	3 (2, 3)	2 (1, 3)	8 (2.5, 15.0)
Senior 2	2 (2, 4)	2 (1, 3)	3 (2, 4)	6 (0, 12)
Senior 3	3 (2, 3)	2 (1, 3)	3 (2, 4)	6 (0, 12)
H	0039	3.391	4.462	1.434
P	0.981	0.183	0.107	0.488

Correlation analysis of level of sport with school adaptability, resilience and cell phone addiction tendency among high school students

Level of sport was positively correlated with school adaptability and resilience ($P < 0.01$); school adaptability was positively correlated with resilience ($P < 0.01$); and cell phone addiction was negatively correlated with sports, school adaptability and resilience ($P < 0.01$) (Table 6).

Table 4 Effect of gender and grade among high school students with medium level of sport

	Intensity	Time	Frequency	Total score
Male	3 (3, 5)	4 (3, 5)	3 (3, 4)	30 (24, 32)
Female	3 (2, 4)	3 (3, 4)	3.5 (3, 4)	24 (24, 36)
Z	0.873	1.144	0.917	0.450
P	0.382	0.253	0.359	0.653
Senior 1	3 (3, 4)	4 (3, 4)	4 (3, 4)	30 (24, 36)
Senior 2	3 (2, 5)	4 (3, 5)	3 (3, 4)	24 (24, 32)
Senior 3	3 (3, 4)	4 (3, 5)	3 (3, 4)	27 (24, 32)
H	0.009	0.436	1.904	2.875
P	0.996	0.804	0.386	0.238

Table 5 Effect of gender and grade among high school students with high level of sport

	Intensity	Time	Frequency	Total score
Male	4 (3, 5)	5 (4, 5)	4 (4, 5)	60 (45, 64)
Female	4 (3, 5)	4 (4, 5)	4 (4, 5)	48 (48, 60)
Z	0.155	0.949	0.268	0.862
P	0.877	0.343	0.788	0.389
Senior 1	4.0 (3.0, 4.5)	5 (4, 5)	4 (3, 5)	48 (45, 60)
Senior 2	4 (3, 5)	5 (4, 5)	4 (4, 5)	50 (48, 62)
Senior 3	4 (3, 5)	5 (4, 5)	4 (4, 5)	60 (48, 64)
H	1.202	0.145	0.095	3.084
P	0.548	0.930	0.954	0.214

Table 6 Correlation analysis of high school students' sports with school adaptability, resilience and cell phone addiction tendency

	Sports	School adaptability	Resilience	Cell phone addiction
Sports	1			
School adaptability	0.761[b]	1		
Resilience	0.765[b]	0.743[b]	1	
Cell phone addiction	-0.747[b]	-0.766[b]	-0.786[b]	1

[b]$P < 0.01$ (two-tailed).

Analysis of the mediating effects of sport and school adaptability, resilience and cell phone addiction among senior high school students

The Bootstrap method was used to test for mediation effect, so as to prove the degree of influence among dependent, independent and mediating variables. The direct effect of sport on cell phone addiction was significant ($P < 0.001$), accounting for 20.51% of the total effect (Figure 3; Table 7). The mediating effect of school adaptability on sport and cell phone addiction was significant ($P < 0.001$), accounting for 17.38% and 35.36% of the total effect value, respectively. School adjustment and resilience had a significant chain-mediated effect between sport and cell phone addiction ($P < 0.001$), accounting for 26.75% of the total effect.

DISCUSSION

We used a field questionnaire survey to collect data on the level of sport, school adaptability, resilience and cell phone

Table 7 Test results of mediating effect

Paths		Coeff	S.E.	LLCI	ULCI
Direct effect	Sports→cell phone addiction	-0.138	0.027	-0.190	-0.085
Indirect effect	(1) Sports→school adaptability→cell phone addiction	-0.117	0.0224	-0.162	-0.0742
	(2) Sports→resilience→cell phone addiction	-0.238	0.025	-0.290	-0.193
	(3) Sports→school adaptability→resilience→cell phone addiction	-0.180	0.017	-0.214	-0.148
	Total indirect effect	-0.536	0.030	-0.598	-0.480
Total effect		-0.673	0.021	-0.714	-0.633

LLCI: Lower limit of 95%CI; ULCI: Upper limit of 95%CI.

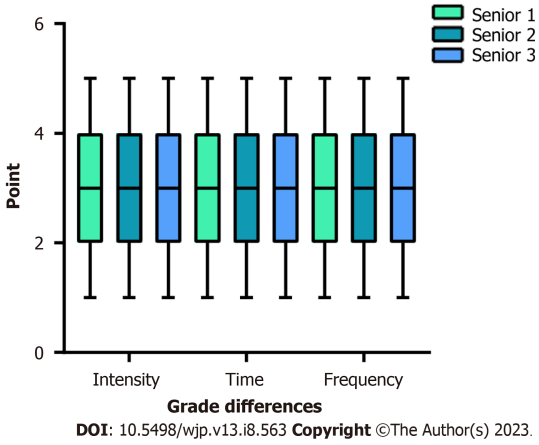

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Figure 1 Differences in level of sport of high school students according to grade.

addiction tendency of senior high school students. Through correlation analysis, a chain mediation effect model was constructed to deeply analyze the influence of sports on school adaptability, resilience and cell phone addiction tendency of senior high school students.

The overall level of sport of high school students reached the medium level, and the level of sport differed significantly by gender, but not by grade. In terms of school adaptability, resilience and cell phone addiction tendency, there were significant differences among low, medium and high levels of sport. There was a positive correlation between level of sport, school adaptability and resilience, and a negative correlation between cell phone addiction and level of sport, school adaptability and resilience. Level of sport had a significant direct effect on cell phone addiction, and school adaptability had a significant mediating effect on level of sport and cell phone addiction. There was a significant mediating effect of resilience between level of sport and cell phone addiction. School adjustment and resilience had significant chain-mediated effects between level of sport and cell phone addiction. Previous studies have shown a significant positive correlation between level of sport and school adaptability[16]. This shows that sports can enhance high school students' adaptability to school, help them establish good interpersonal relationships in school, promote their physical and mental health, and better adapt to the school environment. Similarly, other results show that there is a significant positive correlation between sport and resilience[17], indicating that increasing level of sport is the key to improving the resilience of senior high school students[18]. There was also a significant positive correlation between school adaptability and resilience, indicating that high school students with stronger school adaptability had greater resilience. This is conducive for high school students to cope with various difficulties and setbacks encountered in school or life, and to better complete their studies and develop their social ability in the future[19]. A previous study has shown that sports have a significant negative correlation with cell phone addiction tendency of college students[20], and the results of this study show that sports have a significant negative correlation with cell phone addiction tendency of high school students, which is similar to the results of the present study, indicating that sports can indeed improve the extent of cell phone addiction of senior high school students[21]. Sport can enhance the interpersonal interaction between high school students and their peers, teachers and parents, thus enriching their emotional and social needs, so as to reduce the need to use cell phones for social interaction, thereby preventing cell phone addiction[22]. Analysis of the chain mediation effect model of sport, school adaptability, resilience and cell phone addiction showed that the increase in level of sport improved school adaptability of high school students, and their level of resilience, and reduced their cell phone addiction tendency. Increased level of sport also improved high school students' adaptability or resilience, and reduced their cell phone addiction tendency. Improvement of school adaptability is accompanied by improvement of resilience, which can ultimately reduce cell phone addiction tendency of high school students. Therefore, in order to better develop

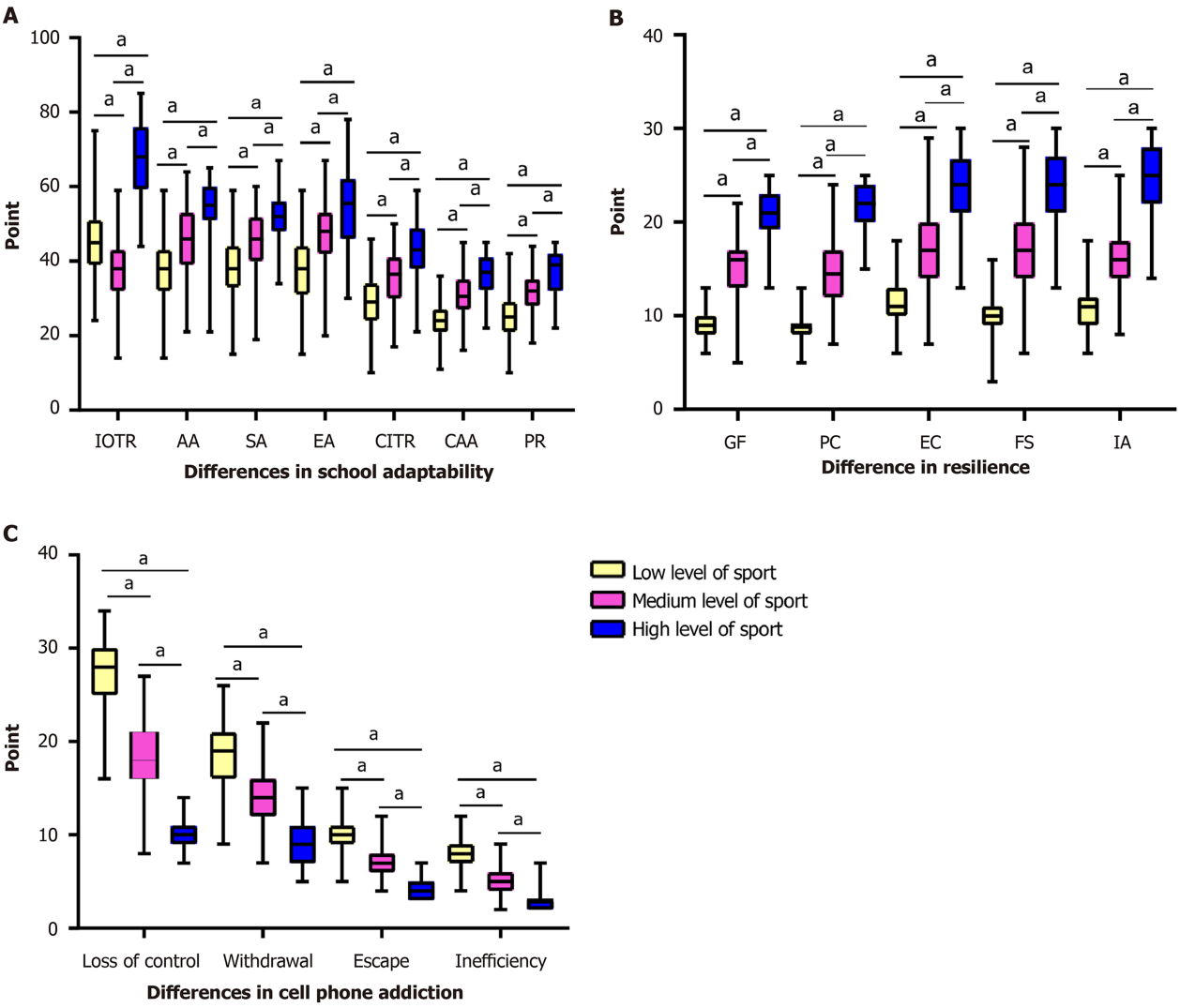

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Figure 2 Effect of low, medium and high levels of sport. A: On school adaptability of high school students; B: On resilience of high school students; C: On cell phone addiction tendency of high school students. $^{a}P < 0.05$. IOTR: Intimacy of teacher-student relationship; AA: Academic adjustment; SA: School attitude; EA: Emotional adjustment; CITR: Conflict in teacher-student relationship; CAA: Class activity adjustment; PR: Peer relationship; GF: Goal focus; PC: Positive cognition; EC: Emotional control; FS: Family support; IA: Interpersonal assistance.

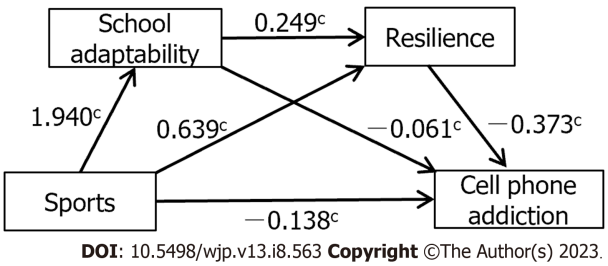

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Figure 3 Chain mediation effect model. $^{c}P < 0.001$.

the mental and physical health of high school students, schools should raise awareness of the importance of sport. Schools should strengthen sports facilities, provide professional guidance and management of sporting activities, and formulate relevant policies to ensure participation in sport, to help high school students participate in school life in a positive manner, eliminate negative emotions, and enhance ability to withstand pressure. Meanwhile, high school students can reduce their dependence on cell phones and improve their physical and mental development[23].

This study had some limitations. The study sample was not comprehensive enough to represent all high school students, so the results have some limitations. The questionnaire survey was a cross-sectional study, which lacked longit-

udinal data and follow-up survey. The longitudinal data and follow-up survey can be combined to further study the relationship between high school students' level of sport, school adaptability, resilience and cell phone addiction tendency, so as to research on the influence of enriching sports on high school students' school adaptability, resilience and cell phone addiction tendency[24,25].

CONCLUSION

Sport can directly affect school adaptability, resilience and cell phone addiction tendency of senior high school students. Sport can affect cell phone addiction tendency through the mediating effect of school adaptability and resilience, and through the chain mediation effect of both.

ARTICLE HIGHLIGHTS

Research background

High school students are in an important stage of physical development. Sport can promote the healthy physical and mental development of high school students, help them adapt to the school environment, relieve study pressure, reduce the level of stress, and reduce cell phone addiction, which are important for healthy physical and mental development.

Research motivation

This study investigated the influence of sport on school adaptability, resilience and cell phone addiction, to establish whether their relationship had a positive impact on the physical and mental development of high school students.

Research objectives

We investigated the relationship between sport and school adaptability, resilience and cell phone addiction tendency in high school students, and the mediating effect of sport was tested. We hope that this study can strengthen high school students' participation in sport, and indicate new ways for improving school adaptability and resilience and reducing cell phone addiction tendency.

Research methods

We collected data using a field questionnaire survey and SPSS was used to analyze the collected data on the effect of sport, school adaptability, resilience and cell phone addiction tendency in senior high school students. Through correlation analysis, a chain mediation effect model was constructed to analyze the influence of sport on school adaptability, resilience and cell phone addiction tendency of high school students.

Research results

Sport, school adaptability and resilience were positively correlated, while cell phone addiction was negatively correlated with sport, school adaptability and resilience, and sport affected the other three through the chain mediation model. The results provide a theoretical basis for further research combined with longitudinal research.

Research conclusions

We conclude that sport has an impact on school adaptability, cell phone addiction tendency and resilience of high school students.

Research perspectives

We analyzed the effect of sport on school adaptability, resilience and cell phone addiction tendency in high school students. In future research, longitudinal research and follow-up can be combined to analyze the relationship among level of sport, school adaptability, resilience and cell phone addiction tendency.

FOOTNOTES

Author contributions: Zhang LQ and Gao HN designed the research; Zhang LQ performed the research and wrote the paper; both the authors reviewed the paper.

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Observational Study

Investigation of contemporary college students' mental health status and construction of a risk prediction model

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Abstract

BACKGROUND

Due to academic pressure, social relations, and the change of adapting to independent life, college students are under high levels of pressure. Therefore, it is very important to study the mental health problems of college students. Developing a predictive model that can detect early warning signals of college students' mental health risks can help support early intervention and improve overall well-being.

AIM

To investigate college students' present psychological well-being, identify the contributing factors to its decline, and construct a predictive nomogram model.

METHODS

We analyzed the psychological health status of 40874 university students in selected universities in Hubei Province, China from March 1 to 15, 2022, using online questionnaires and random sampling. Factors influencing their mental health were also analyzed using the logistic regression approach, and R4.2.3 software was employed to develop a nomogram model for risk prediction.

RESULTS

We randomly selected 918 valid data and found that 11.3% of college students had psychological problems. The results of the general data survey showed that the mental health problems of doctoral students were more prominent than those of junior college students, and the mental health of students from rural areas was more likely to be abnormal than that of urban students. In addition, students who had experienced significant life events and divorced parents were more likely to have an abnormal status. The abnormal group exhibited significantly higher Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 scores than the healthy group, with these differences being statistically significant ($P < 0.05$). The nomogram prediction model drawn by multivariate analysis includ -ed six predictors: The place of origin, whether they were single children, whether

there were significant life events, parents' marital status, regular exercise, intimate friends, and the PHQ-9 score. The training set demonstrated an area under the receiver operating characteristic (ROC) curve (AUC) of 0.972 [95% confidence interval (CI): 0.947-0.997], a specificity of 0.888 and a sensitivity of 0.972. Similarly, the validation set had a ROC AUC of 0.979 (95%CI: 0.955-1.000), with a specificity of 0.942 and a sensitivity of 0.939. The H-L deviation test result was $\chi^2 = 32.476$, $P = 0.000007$, suggesting that the model calibration was good.

CONCLUSION
In this study, nearly 11.3% of contemporary college students had psychological problems, the risk factors include students from rural areas, divorced parents, non-single children, infrequent exercise, and significant life events.

Key Words: College; Predictive models; Psychological health; Risk factors; Logistic regression analysis; Influencing factors

Core Tip: Mental health problems in college students have a marked impact on their physical and mental health, and learning capacity, and are also one of the key issues of concern to educators and society. This study analyzed the mental health status of 40874 college students in selected colleges and universities in Hubei Province, China. A logistic regression model was used to explore the factors affecting the mental health of college students. A risk prediction nomogram model was constructed by R software, which improved the visualization and comprehensibility of the research.

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INTRODUCTION

Mental health refers to all aspects and activities of the psyche that are balanced and harmonious, and is manifested in the individual's correct cognition, good mood, and appropriate behavior[1,2]. Research has demonstrated an annual yearly increase in the detection of psychological health issues among college students over the last three years[3], indicating that this problem has attracted more and more attention. In 2017-2018, a white paper study on the mental health of Chinese urban residents showed that 73.6% of the college students surveyed had sub-health status. This problem requires attention in order to be resolved. College students are the backbone of the future of society[4]; with the development of the social economy, competition is becoming increasingly fierce, and the mental health of these students has attracted extensive attention from society and schools[5]. University students are in the transition stage between school and society, and their mental health is highly susceptible to pressure from all sides. Most of the studies on the mental health of college students have mainly focused on the main influencing factors, and there are few studies on risk prediction analysis[6,7]. However, the diversity, complexity, variability, contingency, and uncertainty of college students' mental health problems pose challenges in mental health risk prediction. Therefore, constructing a risk prediction model is conducive to screening mental health problems, preventing and treating risk factors for disease occurrence, and reducing morbidity. This study determined the mental health of current college students using a questionnaire survey. Based on an analysis of influencing factors, a mental health risk prediction model for college students was constructed using logistic regression, which provided a reference for counseling college students' mental health problems in the future, which was conducive for providing better mental health care for college students.

MATERIALS AND METHODS

General information

All college students in some of the universities in Hubei Province were selected as research subjects. An online questionnaire survey was conducted from March 1 to 15, 2022, and the questionnaires were distributed using QQ and WeChat. Based on the principle of voluntariness, the respondents completed the questionnaire after scanning the QR code. Each IP address can only be registered to answer once to ensure the quality of the questionnaire. After the investigation, a total of 41610 survey forms were acquired, of which 40874 data were used, and the effective response rate was 98.2%. In these valid data, girls accounted for 45.4% (18547) and boys accounted for 54.6% (22327). A random sampling method selected 2% of valid questionnaires from 40874 valid data.

Research methods

The general questionnaire included data on age, grade, gender, family situation, academic performance, major life events, and other social demographic data. Using the symptom self-rating scale (SCL-90)[8,9], a total of 90 items were scored at 5 levels (0-4), with scores ranging from 0 (none) to 4 (severe); the scale is divided into physical status, interpersonal sensitivity, obsessive-compulsive symptoms, anxiety, depression, hostility, paranoia, terror, psychosis and another 10 symptoms. This scale is commonly used in mental health screening tools due to its comprehensiveness and ease of understanding. The Patient Health Questionnaire (PHQ-9)[10,11] was used to evaluate depression in college students. There were 9 criteria in total and the scoring ranged from 0 (never) to 3 (almost every day). The total score was the sum of the scores of each item (0-27 points). The score was divided into 5 levels (no depression to severe depression): 0-4, 5-9, 10-14, 15-19, and 20-27. Assessment of generalized anxiety symptoms was carried out using The Generalized Anxiety Disorder score[5], with a total of 7 items (0-3 points: From none to almost always), 4 levels of the total score 0-21 points (no anxiety to severe anxiety: 0-4, 5-9, 10-14, 15-21), and the higher the score, the more pronounced the anxiety state.

Statistical analysis

Statistical analysis was conducted using SPSS23.0 software. The experimental data obeyed normal distribution, expressed as mean ± SD in terms of homogeneity of variance, and were compared by independent samples *t*-test. Count data were expressed as n (%) using the χ^2 test; data with a value of $P < 0.05$ were considered statistically significantly different. Single-factor analysis was performed with SPSS23.0, and logistic regression was used for multivariate analysis of statistically significant variables. The prediction model was then constructed, and a nomogram model was constructed using R4.2.3. This research used the receiver operating characteristic (ROC) curve to predict the model performance and used the H-L to test the goodness of fit of the model.

RESULTS

Sample characteristics

We randomly selected 918 cases consisting of 2% of the valid data, including 814 cases in the mental health group and 104 cases in the abnormal mental health group. The incidence of mental health abnormalities was 11.3%. Educational background, place of origin, parent's marital status, whether they were single children, whether they had significant life events, and whether they had intimate friends showed statistical significance ($P < 0.05$) (Table 1).

Logistic regression analysis

Logistic regression analysis was performed to determine whether mental health was abnormal as the dependent variable (mental health = 0, mental health abnormality = 1) and independent variables comprising factors with a significant statistical correlation or association in single-factor analysis (Table 2). The results showed that parents who were divorced/widowed, non-single children, major life events, infrequent exercise, and no close friends were independent risk factors for mental health abnormalities in college students ($P < 0.05$) (Table 3).

Construction of the nomogram model and validation of its predictive performance

Based on the independent factors in the regression model (education, place of origin, exercise, parents' marital status, close friends, and whether major life events occurred), variables with significant differences ($P < 0.05$) were included and a nomogram model was constructed (Figure 1). The Bootstrap method was used to verify the model. The results of the H-L deviation test were $\chi^2 = 32.476$, $P = 0.000007$, suggesting that the model exhibited favorable calibration. According to the training set, the area under the ROC curve was 0.972 [95% confidence interval (CI): 0.947-0.997], and the specificity and sensitivity were 0.888 and 0.972, respectively. The validation set ROC area under the (AUC) was 0.979 (95%CI: 0.955-1.000), with a specificity of 0.942 and a sensitivity of 0.939. In the training set, the nomogram-based prediction model yielded a mean absolute error (MAE) of 0.01, and the mean square error (MMSE) was 0.00022. The MAE of the validation set was 0.007, and the MMSE was 0.00026. The smaller the statistics, the higher the calibration of the prediction model (Figures 2 and 3).

DISCUSSION

University is an important stage in the life of college students and a crucial period for personality completion and self-improvement[12]. College students are active and accept a wide range of information but do not have complete psychological defense abilities. They are easily disturbed by external factors, causing anxiety, panic, and other negative emotions, resulting in blind conformity and impulsive behavior. For college students, entering university means they are about to enter society. At this crossroad, they face pressure and confusion due to learning, love, employment, and family. These aspects of stress, to a certain extent, affect the psychological health of college students[13]. Due to the increased risk of mental health problems, mental health research has become a priority for many scholars[14]. Studies have found that different nationalities, genders, grades, only children, different subjects, and different school types are all related to the mental health of college students[15]. In addition, some studies have found that only children, parental relationships, and domestic violence directly affect the mental health of college students[16]. These results are not entirely consistent with those of this study. This phenomenon can be explained by the vulnerability of mental health to environmental/social

Table 1 Univariate analysis of the mental health of contemporary college students

Variables	Grouping	Healthy, *n* = 814	Abnormal, *n* = 104	Statistic	*P* value
Age (mean ± SD)		22.98 ± 3.02	23.12 ± 3.16	0.443	0.658
Education, *n* (%)	Specialized	42 (87.50)	6 (12.50)	8.684	0.034
	Undergraduate	629 (92.36)	52 (7.64)		
	Master	116 (76.32)	36 (23.68)		
	Doctor	27 (72.97)	10 (27.03)		
Gender, *n* (%)	Female	317 (90.06)	35 (9.94)	0.952	0.329
	Male	497 (87.81)	69 (12.19)		
Native place, *n* (%)	Countryside	308 (82.35)	66 (17.65)	25.079	< 0.001
	City	506 (93.01)	38 (6.99)		
Nationality, *n* (%)	Han	720 (88.45)	94 (11.55)	0.308	0.579
	Ethnic minority	94 (90.38)	10 (9.62)		
Education level of parents, *n* (%)	Junior high school and below	500 (87.11)	74 (12.89)	5.361	0.069
	Senior high school/technical secondary school	223 (89.92)	25 (10.08)		
	College and above	91 (94.79)	5 (5.21)		
Have major life events occurred, *n* (%)	Yes	36 (36.73)	62 (63.27)	153.396	< 0.001
	No	778 (94.88)	42 (5.12)		
Academic record, *n* (%)	Excellent	38 (86.36)	6 (13.64)	5.378	0.146
	Good	246 (88.81)	31 (11.19)		
	Moderate	493 (89.64)	57 (10.36)		
	Poor	37 (78.72)	10 (21.28)		
Parental marital status, *n* (%)	Normal	622 (93.96)	40 (6.04)	64.313	< 0.001
	Divorced/widowed	192 (75.00)	64 (25.00)		
Only child, *n* (%)	Yes	633 (93.92)	41 (6.08)	69.467	< 0.001
	No	181 (74.18)	63 (25.82)		
Underlying disease, *n* (%)	Yes	698 (87.91)	96 (12.09)	3.306	0.069
	No	116 (93.54)	8 (6.46)		
Take regular exercise, *n* (%)	Yes	371 (93.92)	24 (6.08)	19.054	< 0.001
	No	443 (84.70)	80 (15.30)		
Close friends, *n* (%)	Yes	493 (94.63)	28 (5.37)	42.524	< 0.001
	No	321 (80.86)	76 (19.14)		
PHQ-9 (mean ± SD)		36.29 ± 3.59	42.59 ± 4.35	99.409	< 0.001
GAD-7 (mean ± SD)		32.16 ± 8.13	35.24 ± 6.78	52.650	< 0.001

PHQ: Patient Health Questionnaire; GAD: Generalized Anxiety Disorder.

conditions. A survey conducted in the United States found that more than one-third of students suffered from depression, while between 2007 and 2008, approximately 10 percent of college students were found to have considered suicide[17]. According to a study conducted in China in 2010, approximately 10% to 30% of university students were affected by mental health issues, which aligns with the findings of this research. According to the National Mental Health Development Report of China (2019-2020), 18.5% of college students tend towards depression, 4.2% have a high risk of depression, and 8.4% have an anxiety tendency. A sample survey by the former State Education Commission found that 20.3% of college students have psychological problems. The above research results are not entirely different to the results in this study.

Our findings show that parental' divorce/widowhood is a risk factor affecting college students' mental health [odds ratio (OR) = 5.628, (95%CI: 2.450-12.927)]. Family is the crucial environment for personal growth. The family atmosphere

Table 2 Independent variable assignment

Variables	Assignment
Education	Specialized = 0
	Undergraduate = 1
	Master = 2
	Doctor = 3
Only child	No = 1
	Yes = 0
Native place	Countryside = 1
	City = 0
Have major life events occurred	No = 0
	Yes = 1
Take regular exercise	No = 1
	Yes = 0
Parental marital status	Normal = 0
	Divorced/widowed = 1
Close friends	Yes = 0
	No = 1
PHQ-9	Primitive value input
GAD-7	Primitive value input

PHQ: Patient Health Questionnaire; GAD: Generalized Anxiety Disorder.

Table 3 Logistic regression analysis of the influencing factors on college students' mental health

Variables	β	SE	Wald	*P* value	OR (95%CI)
Education			12.166	0.007	
1	-2.449	1.173	4.357	0.037	0.086 (0.009-0.861)
2	-2.507	0.725	11.957	0.001	0.081 (0.020-0.337)
3	-1.974	0.795	6.168	0.013	0.139 (0.029-0.660)
Native place	1.131	0.419	7.290	0.007	3.099 (1.363-7.043)
Exercise	-2.380	0.554	18.439	0.068	0.093 (0.031-0.274)
Parents' marriage	1.728	0.424	16.597	< 0.001	5.628 (2.450-12.927)
Non-only child	3.616	0.583	38.489	< 0.001	37.175 (11.862-116.500)
Significant events	3.706	0.498	55.318	< 0.001	40.709 (15.329-108.111)
No close friends	1.563	0.443	12.424	< 0.001	4.773 (2.002-11.384)
PHQ-9	0.530	0.061	48.915	< 0.001	1.537 (1.363-1.734)
GAD-7	0.055	0.025	4.014	0.045	1.051 (1.001-1.103)
Constant	-22.220	2.895	58.096	< 0.001	0.000

PHQ: Patient Health Questionnaire; GAD: Generalized Anxiety Disorder; OR: Odds ratio; CI: Confidence interval.

significantly relates to the formation of a person's personality[18] and impacts personal psychological development. A large number of research surveys have shown that family has a significant impact on students' mental health[19,20]. A good family environment is conducive to college students' physical and mental health[21], which can reduce the risk of abnormal mental health. An unhealthy family environment (*e.g.*, parental divorce or widowhood, family conflicts) can

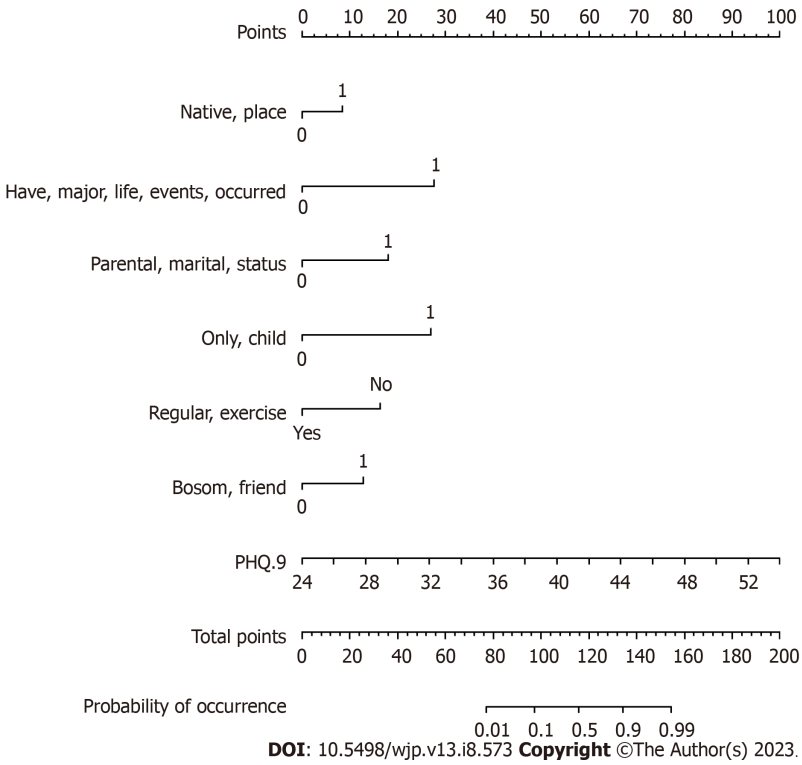

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Figure 1 Risk nomogram prediction model of college students' mental health status. PHQ: Patient Health Questionnaire.

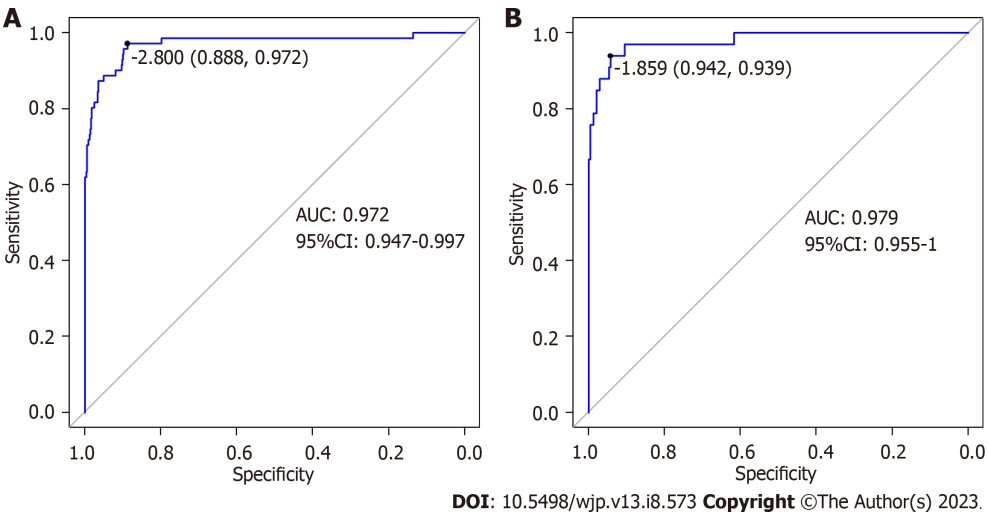

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Figure 2 Column chart prediction model receiver operating characteristic curve. A: Receiver operating characteristic (ROC) curve of the training set; B: ROC curve of the validation set. AUC: Area under the curve; CI: Confidence interval.

easily lead to abnormal mental health in college students and even result in students forming bad personalities[22].

Similarly, studies have shown that parental separation is a risk factor for college students' mental health issues[23]. Domestic and foreign research shows that parental relationships affect children's growth and mental health. Paying attention to the influence of parental relationships on college students' mental health and providing improvement strategies can enable parents to play a role in promoting their mental health.

The present study showed that students from rural areas had an increased risk of mental health issues (OR = 3.099, 95%CI: 1.363-7.043). These results are consistent with those of Zhang and Qi[24]: In terms of psychological stress, college students from rural areas have a significantly higher risk than those from urban areas. These results were related to the rural family's economic environment and cultural atmosphere. Due to differences in resources, the economic conditions of college students from rural areas are worse than those from urban areas. In particular, students from rural areas studying in large cities, have higher living expenses. Some families do not have stable economic sources, and their economic deficiencies and life pressure make them prone to inferiority[25].

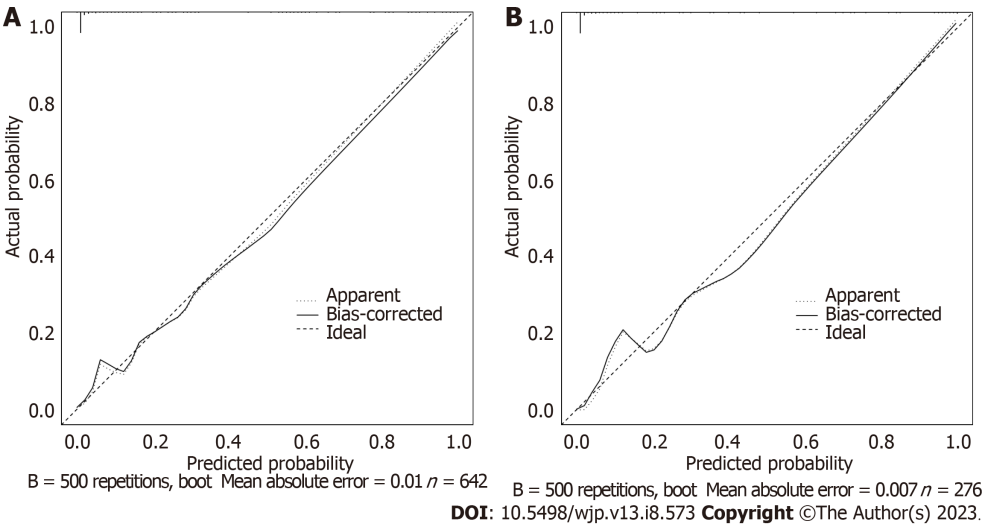

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Figure 3 Column chart prediction model calibration curve. A: Calibration curve of the training set; B: Calibration curve of the validation set.

A significant correlation exists between critical life events and the psychological health of university students. In this study, major life events were a risk factor for mental health problems in college students (OR = 40.709, 95%CI: 15.329-108.111). Due to their limited exposure to social and real-life situations, college students are often confined within a sheltered campus environment, lacking sufficient life experience, exhibiting immature cognition, and having insufficient capacity to effectively cope with psychological stressors. When faced with adverse events or unforeseeable circumstances, such as natural disasters or family tragedies, their psychological resilience will be significantly challenged, potentially leading to psychological distress and impediments.

This study showed that regular exercise was a protective factor for mental health (OR = 0.093, 95%CI: 0.031-0.274). Relevant studies have found that moderate physical exercise has a more significant impact on mental health than non-exercise[26]. Fossati *et al*[27] found that participating in sports and exercise benefits an individual's mental state and can improve mood and quality of life. Herbert[28] found that physical activity and exercise help to promote the mental health of emerging adults such as college students. Huang[29] used the intelligent health system to assess the health status of college students before and after dance exercises. The results showed that the mental health of college students participating in dance exercises increased by 7.8%, indicating that sports and dance can promote physical and mental health. Thus, regular exercise can not only promote physical health but also help to improve mental health.

According to the findings of this investigation, a single child has a good mental health status, and being a non-single child is a risk factor for college students' mental health (OR = 37.175, 95%CI: 11.862-116.500). These results are quite different from existing research. Cheng *et al*[30] and others found that the incidence of emotional distress characterized by feelings of unease, apprehension, and low mood in non-single children was higher than that in single children in college and university students from Jinan, Shandong. The reason for this may be that the survey areas were different, and the results do not represent the mental health status of all college students. This may be because most of the single children come from cities, their parents have relatively high educational levels, and their family economic situations are better than those of non-single children. In the one-child family, parents will meet their wishes as much as possible, pay more attention to their education, and get help when they encounter problems. Most of the non-single children were from rural areas, with relatively poor economic conditions and a sense of inferiority[31]; because there are other siblings in the family, parents pay less attention to each child and do not pay attention to communication with their children, resulting in some non-single children encountering problems that cannot be solved and thus affects their mental health.

The findings from this investigation indicated a higher likelihood of psychological problems among college students who lack close friends compared to those who have intimate companions, and was a risk factor for college students' mental health (OR = 4.773, 95%CI: 2.002-11.384). The results by Li *et al*[32] proved this view. Research also shows that good friendships can help people alleviate negative psychology and provide emotional support[33]. The survey by Abraham and Sher[34], it was found that a solid interpersonal relationship was a protective factor against adolescent suicide, which was in line with the findings obtained from the current research: The existence of intimate friends was a protective factor for college students' mental health. In the face of difficulties and pressure, good friends will help and care about each other, which can reduce psychological pressure and is conducive to good mental health. Therefore, getting along with or having close friends is necessary.

The individual is central in resolving their psychological issues. First, they need to develop a scientific understanding of health, proactively foster positive psychological traits, gain accurate comprehension and acceptance of themselves, sustain a favorable emotional outlook, engage with loved ones and acquaintances as support systems when confronting challenges, and cultivate a fully-rounded and harmonious state of health. Secondly, strive to actively acquire and master the techniques for recognizing psychological issues and practicing self-regulation. Individuals should actively exercise, participate in social activities, enrich life experiences, increase social experience, and improve their ability to resist pressure.

Universities and colleges should integrate mental health education into their talent development paradigm by designing courses, organizing psychological quality training sessions, and establishing psychological counseling rooms, among other methods. This would enable college students to acquire knowledge on mental health, enhance their psychological adjustment abilities, and effectively address various psychological issues. In so doing, college students can access timely and effective assistance and guidance during any psychological crises that they may encounter.

Parents ought to lead by example by creating a favorable family environment that fosters effective communication and mutual respect while prioritizing the emotional well-being of their offspring. To achieve this, parents should eagerly listen to their children's emotional needs, encourage them to express themselves fully, and form a close-knit bond with them. They should also aim to foster home-school cooperation towards safeguarding the mental health of college-going students.

CONCLUSION

According to the results of this study, the current college students show a good state in mental health. By using the sample set data of the mental health risk prediction model and modeling and processing it, we provide an important reference for the prevention and intervention of college students' mental health problems. The data obtained from this research is singular, and sourced from a specific region with a limited sample size. As mental health depends on the environment, the representativeness of the sample may have specific limitations. Therefore, it is essential to enhance the model through prospective, multi-center studies with a sufficient sample size.

ARTICLE HIGHLIGHTS

Research background

Mental health problems in college students have become the focus of academic and social attention. The main reason is that college students are facing many pressures and challenges, such as academic pressure, social pressure, career planning pressure, and so on. In addition, the rapid development of modern society and the competitive environment have also brought new challenges and threats to the mental health of college students. Therefore, the study of college students' mental health has profound practical significance and theoretical value.

Research motivation

With the increasing pressure and challenges faced by college students, their mental health problems are becoming more and more serious, and the detection rate is increasing yearly.

Research objectives

Research on the mental health status of current college students and the construction of a risk prediction model can not only help us to understand the mental health problems faced by college students more comprehensively, but also provide a valuable reference for prevention strategies. It can also identify and intervene in mental health problems at an earlier time point to avoid further deterioration of the problem. In addition, future research in this field can also explore the relationship between mental health status and college students' learning, life, and interpersonal communication, and provide useful support for improving the overall quality and development of college students.

Research methods

The objective of the current research was to examine the mental well-being of 40874 undergraduate and graduate students enrolled in various higher education institutions within a particular geographical area. Additionally, using logistic regression analysis, the determinants that exert a substantial influence on the psychological health of university students were investigated. This model has high accuracy and interpretability. This study used R software to construct a risk prediction nomogram model, which enabled researchers to understand the influence and relationship of different variables more intuitively and improved the visualization and comprehensibility of the research. In summary, this study adopted a variety of advanced research methods, which had a wide range of reference values and application prospects.

Research results

The survey found that 11.3% of college students had psychological problems. The risk factors for college students' mental health include being from rural areas, non-single children, major life events, parents' marital divorce, infrequent exercise, and no close friends. The area under the receiver operating characteristic (ROC) curve in the training set was 0.972, the specificity was 0.888, and the sensitivity was 0.972. The area under the ROC curve in the validation set was 0.979, the specificity was 0.942, and the sensitivity was 0.939. These findings reflect the current mental health status of college students and is of great significance for the public to raise attention and awareness of mental health problems. It provides a basis for the government and schools to formulate mental health policies and help to formulate effective mental health management measures. At present, there are still some problems in the design and application of college students' mental health questionnaires, as some students could not understand or answer the questions in the questionnaire. More comprehensive and in-depth analysis and research are still needed to ensure the accuracy and reliability of the analysis

and statistical results.

Research conclusions

From this research, we conclude that the current mental health status of college students is good. New methods used in this study include the use of a logistic regression model and the use of R software to construct a risk prediction nomogram model to explore the related factors affecting the mental health of college students. These methods can predict the risk factors related to college students' mental health more accurately and provide more effective intervention measures and prevention methods.

Research perspectives

Assessing and monitoring the mental health of college students can help schools and other institutions to better understand the needs of college students and take timely measures to prevent the emergence of mental health problems. Future research should focus on developing more effective assessment tools and establishing tracking and monitoring systems.

FOOTNOTES

Author contributions: Mao XL designed and performed the research and wrote the paper; Chen HM designed the research and contributed to the analysis.

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

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

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L-Editor: A
P-Editor: Wang JJ

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ORIGINAL ARTICLE

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Effect of cognitive behavioral group therapy on rehabilitation of community patients with schizophrenia: A short-term randomized control trial

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Abstract

BACKGROUND

The efficacy of cognitive behavioral group therapy (CBGT) for cognitive dysfunction and negative symptoms of schizophrenia is established, but more evidence is required.

AIM

To assess the effectiveness of CBGT combined with mental health education as a treatment for schizophrenia compared with mental health education alone.

METHODS

In all, 120 schizophrenia out-patients were randomized into CBGT combined with mental health education or single mental health education. The primary outcomes were positive and negative symptoms, cognitive function, excitatory factor, anxiety and depression symptom improvements on the positive and negative syndrome scale score. Secondary outcome measures included social function and drug compliance.

RESULTS

There were significant differences between CBGT combined with mental health education and single mental health education on measures of positive and negative symptoms, cognitive functions, excitatory factor, anxiety and depression symptoms, and social functions. No other significant difference in outcomes was

observed.

CONCLUSION
CBGT combined with mental health education may be relevant beneficial treatment method in reducing symptoms, cognitive and social functions of patients with schizophrenia.

Key Words: Schizophrenia; Cognitive behavioral group therapy; Family members; Social functions; Mental health; Community; Psychological intervention

Core Tip: Psychological therapies for schizophrenia still deserves to be explored due to its advantages of having comparatively fewer side effects. As one of the different psychological approaches, cognitive behavioral therapy has been proven to be effective in the treatment of schizophrenia with sound evidence. This study provides new insights by adding cognitive behavioral group therapy to the conventional pharmaceutical therapy plus mental health education for the treatment of schizophrenia. It also provides some guidance on developing community rehabilitation models in patients with mental illness.

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INTRODUCTION

Schizophrenia is a serious mental disorder, which can lead to loss of personality, decline in social function and the state of mental disability in various levels. Negative symptoms and cognitive impairment have been found to have a profound impact on long-term outcomes of schizophrenia, but current treatment options are limited. Recent studies have shown that the combination of cognitive behavioral group therapy (CBGT) can improve patient compliance with drug therapy, alleviate psychotic symptoms, reduce recurrence and rehospitalization rates, and improve social function and quality of life in schizophrenia.

This study aims to evaluate the impact of CBGT combined with mental health education on the clinical symptoms, cognitive and social functions and psychological status in patients with schizophrenia on the basis of conventional drug treatment, so as to provide evidence for its application to community rehabilitation for patients with schizophrenia.

MATERIALS AND METHODS

Participants

This was a randomized control trial approved by the Biomedical Ethics Review Committee of Longhua District Chronic Disease Prevention and Treatment Center (Mental Health Center), and obtained the informed consent of family members of the research patients. Participants were recruited from outpatients with schizophrenia. The inclusion criteria included diagnosis of schizophrenia (ICD-10 codes F20.0 to F20.9); 1 to 5 years of disease course with a stable condition; presence of dangerous behavior involving verbal threats; no obvious vandalism; partial recovery of self-knowledge; positive score for positive and negative symptom scale (PANSS) ≤ 49 or negative scale score ≤ 49; social function deficiency screening scale (SDSS) score ≥ 2; aged 19 to 60 years old; higher levels of education than primary school; with at least one guardian; taking second-generation antipsychotics for ≥ 1 year. Inclusion criteria for family members was those who have no mental history. Patients with co-morbidities, other psychiatric disorders (*e.g.*, organic disorders, psychoactive substance-induced psychiatric disorders) or serious physical disorders affecting cognitive functions and family members with speech impairment were excluded from this trial.

Study design

Randomization was conducted using computer-generated random numbers with 120 participants allocated in blocks. These patients were randomly allocated to an intervention group and a control group with 60 patients in each group. The intervention group was subdivided into four groups with 15 patients and their family members in each group receiving CBGT combined with mental health education for 8 wk. The interventions in each group were led by an experienced psychiatrist or psychotherapist trained in CBGT. The control group was only given mental health education courses for 8 wk. The study was reviewed and approved by the Biomedical Ethics Review Committee of the Shenzhen Longhua District Chronic Disease Control Centre (Mental Health Centre) and informed consent was obtained from patients'

families.

Intervention programs

CBGT intervention is divided into four stages: (1) Stage 1 (the first time): The initial stage. The basic task is acceptance and commitment. Members and team leaders get to know each other, understand the troubles in each other's life and communicate with each other, normalize problems, introduce CBGT to group members, set group contracts, set group goals and enhance group cohesiveness; (2) Stage 2 (2^{nd}-3^{rd}): *i.e.*, transition stage. Assist group members to deal with their emotional reactions and conflicts, and promote trust and relationship building. Identify the situations that induce stress and emotional conflicts, and perceive the related assumptions of situations, ideas, emotions and behaviors constructed under the stress situation; Identify and evaluate symptoms and negative cognitions; Examine the evidence to repair negative cognitions, core beliefs and dysfunctional assumptions. In addition, this stage also includes relaxation training, role play, imitation demonstration, resolving emotional conflicts such as anxiety and depression, seeking resource support and increasing self-confidence; (3) Stage 3 (4^{th}-7^{th}): *i.e.*, working stage. Further explore problems and take effective actions to promote the change of members' behaviors. Through psychological education and social skill training, encourage members to observe and imitate, consolidate self-monitoring and self-guidance training during rehabilitation, change distorted thinking patterns and improve self-esteem; and (4) Stage 4 (8^{th}): The end stage. Summarize group experiences, consolidate achievements, encourage team members to use learning experiences in life, solve problems and emotional conflicts, enhance self-confidence, inject hope, and deal with parting emotions.

Outcome measures

The participants were randomly divided into an intervention group (60 cases) and a control group (60 cases). Each patient had his/her one family member to participate in the trial. In addition to antipsychotics and mental health education implemented in the community, patients in the intervention group received CBGT together with their guardians for 8 wk. Patients in the control group only received antipsychotic drugs and mental health. Patient social functions, symptoms of schizophrenia and activities of daily living (ADL) were evaluated by SDSS, PANSS and ADL scale before CBGT treatment, 8 wk and 4 wk after the treatment (*i.e.*, before the intervention, after the intervention and 4 wk after the intervention, respectively). According to the evaluation results of the scale at three time points, the intervention effects of CBGT on patient symptoms and social functions were analyzed.

Primary outcome measures

Primary outcome measures include improvements in symptoms measured by the scale of the PANSS. Using the positive and negative symptom scale, five-factor dimensions of Chinese norm were evaluated: Positive factor, negative factor, cognitive factor, excitatory factor, anxiety and depression factor. Social function is evaluated by SDSS scale.

Two psychiatrists scored 10 patients using PANSS scale, and calculated kappa coefficient = 0.822 through SPSS 22.0. The evaluation of the two doctors is in good agreement and has high consistency.

Secondary outcome measures

The ability to live was assessed by the ability of daily living scale. Medication compliance was evaluated from three types: (1) Complete compliance: Completely follow the doctor's advice for one month; (2) part compliance: Taking medicine for more than 33% course of treatment in a month; and (3) non-compliance: 33% course of treatment in a month with no medication.

Statistical analysis

Statistical analysis was conducted using the SPSS 22.0 software. The rank-sum test and sample independent *t*-test were used for the variable data, and the chi square test was used for the categorical data. Repeated measures ANOVA was used to determine the effects of different intervention modalities on patients' clinical symptoms, social functioning, abilities to perform daily living activities and medication adherence at three different time points: Pre-intervention, post-intervention and 4 wk post-intervention. By analysis of studentized residuals, the data in each group had no outliers (≥ ± 3SD) and followed a normal distribution ($P > 0.05$) according to the Kolmogorov-Smirnov test. The conditions for the sphericity test must be satisfied so that the data could be tested for normality and symmetry with sphericity, and in case the assumption for sphericity was not met, the method of Greenhouse-Geisser (G-G) for correction was used. The test level of $P < 0.05$ was considered statistically significant. It was then determined whether there was an interaction between factors (groups and time points) in the intervention group and the control group. If there was an interaction, *t*-test and one-way ANOVA were required to determine whether there was a separate effect. When a separate effect test was required, test level of $P < 0.05$ was considered statistically significant. If there was no interaction, a main effect test was required to determine whether there was a main effect, with a test level of $P < 0.05$ being statistically significant. A two-by-two comparison was carried out. We used Bonferroni correction for multiple repeated ANOVA testing.

RESULTS

After the treatment and at 4-wk follow-up, none of the 120 patients dropped out.

Participant characteristics

Patients with schizophrenia in both groups had a disease course of 1 to 5 years and were in stable condition. They were treated with second-generation antipsychotics in the community. General data show that the average age of them is 38 years old. There were slightly more women (53.33%) than men (46.67%) in the intervention group, and there were more men (61.67%) than women (38.33%) in the control group. The educational background for the participants is mainly below junior high school. There was no significant difference in age, gender, education level, medical burden and family income between the intervention group and the control group. The baseline characteristics of the participants are presented in Table 1.

The general data (age, gender, education level, medical burden, annual family income) of the family members were analyzed and compared in the two groups. There was no significant difference in general data between the two groups ($P > 0.05$). The baseline characteristics of the sample are presented in Table 2.

Primary outcomes

The overall PANSS score, positive factor score, cognitive factor score, excitatory factor score, anxiety and depression factor score and SDSS score decreased successively in the two groups at three time points. After the intervention and at four weeks after the intervention, the overall PANSS score ($P < 0.05$ and $P < 0.001$, respectively), positive factor score ($P > 0.05$ and $P < 0.001$, respectively), cognitive factor score ($P < 0.05$ and $P < 0.001$, respectively), excitatory factor score ($P > 0.05$ and $P < 0.001$, respectively), the scores of anxiety and depression factors ($P > 0.05$ and $P < 0.001$, respectively) and the overall score of SDSS ($P < 0.01$ and $P < 0.01$, respectively) were significantly different from those before the intervention. After repeated measurement analysis of variance, there was interaction between group and time points in the total overall score of SDSS ($P < 0.05$). After the intervention, there were significant differences between the intervention group and the control group in PANSS total score ($P < 0.05$), positive factor score ($P < 0.05$), cognitive factor score ($P < 0.05$) and SDSS total score ($P < 0.01$). At four weeks after the intervention, there were significant differences between the intervention group and the control group in PANSS total score ($P < 0.01$), excitation factor score ($P < 0.05$), cognitive factor score ($P < 0.01$), anxiety and depression factor score ($P < 0.01$) and SDSS total score ($P < 0.01$). Outcomes are shown in Table 3 and Figure 1.

Secondary outcomes

χ^2-test was performed for medication compliance in the two groups at three time points. The results showed that there was no significant difference between the intervention group and the control group before the intervention ($P > 0.05$). There was no significant difference in medication compliance between the two groups after the intervention and at 4 wk after the intervention ($P > 0.05$). Compared with the control group, the proportion of complete compliance in the intervention group increased slightly (8.34%) after the intervention (83.33%) and at 4 wk after the intervention (91.67%) as presented in Table 4.

DISCUSSION

This is a study to evaluate the effect of CBGT combined with mental health education on community-based rehabilitation of patients with schizophrenia. The main results showed that: (1) Compared with the control group, patients in the intervention group had significantly lower PANSS total scores and five factor scores post-intervention, with negative factor and cognitive factor scores still showing reduction at 4 wk post-intervention; (2) SDSS scores in the intervention group significantly decreased; (3) ADL scores decreased in both groups after the intervention and at 4 wk after the intervention, and the difference was not significant; and (4) there was no significant difference in medication adherence between the intervention group and the control group.

Our findings confirm the ameliorative effect of CBGT on the psychotic symptoms of patients with schizophrenia. Combined with the current situation of community psychiatric rehabilitation management in Shenzhen, the participants of this study are migrant workers in Shenzhen, and as general information shows, this group of population has a low level of education, and nearly half of them do not purse education beyond junior high school with a household income of around 40000 CNY. The migrant workers have medical and social resources availability is restricted and have received relatively little social support. Therefore, the aim of this study is to explore a feasible community-based rehabilitation model for migrant workers. In this study, a comparative analysis of psychiatric symptoms using the five-factor dimension of the PANSS scale Chinese normative model found that 8 wk of CBGT combined with mental health education significantly improved the patients' clinicopathological symptoms and remained effective in improving negative symptoms and cognitive dysfunction after 4 wk of follow-up.

Previous studies have reported inconsistent results on the effectiveness of CBGT in improving positive and negative symptoms of schizophrenia, possibly because different studies have used different evaluation criteria and intervention cycles[1-11]. This study was completed using a modified short-term CBGT format in patients with schizophrenia and their family members, and explored together with patients the reasons for their laziness and reluctance to think and communicate, which were often related to their automatic thoughts such as "I am a useless person", "I will not be welcomed by anyone", "things outside are not interesting", *etc*. Behavioral tests are used, *e.g*. developing a behavioral plan to test the validity of one's beliefs, *e.g*. encouraging one to recall his/her pre-morbid state, self-affirming exceptions and increase self-confidence. When distressing experiences such as hallucinations and delusions of "if I go out, I'll get hurt", coping strategies such as self-symptom monitoring logs and problem solving support are used to alleviate patient feelings of unease and surveillance towards the external environment. Patients are encouraged to think about how they

Table 1 Patient characteristics, *n* (%)

Variables	Control group (*n* = 60)	Intervention group (*n* = 60)	t/χ^2	*P* value
Age (yr)	37.95 ± 10.33	38.47 ± 10.68	0.269	0.788
Gender			2.719	0.099
Male	37 (61.67)	28 (46.67)		
Female	23 (38.33)	32 (53.33)		
Educational level			5.967	0.113
Primary school	10 (16.67)	13 (21.67)		
Junior high school	40 (66.67)	29 (48.33)		
Technical secondary school/high school	8 (13.33)	10 (16.67)		
College/undergraduate	2 (3.33)	8 (13.33)		
Medical burden (CNY)	3300 ± 2700	3000 ± 1600	-0.865	0.389
Annual household income (CNY)	45200 ± 32800	38500 ± 29200	-1.178	0.241

The variable data adopts *t*-test, and the attribute data adopts χ^2 test, n = 60. There was no significant difference between the intervention group and the control group ($P > 0.05$).

Table 2 Family member characteristics, *n* (%)

Variables	Control group (*n* = 60)	Intervention group (*n* = 60)	t/χ^2	*P* value
Age (yr)	43.02 ± 10.44	42.38 ± 9.40	-0.349	0.727
Gender			2.344	0.126
Male	35 (58.33)	43 (71.67)		
Female	25 (41.67)	17 (28.33)		
Educational level			9.226	0.026
Primary school	3 (5.00)	13(21.67)		
Junior high school	40 (66.67)	32 (53.33)		
Technical secondary school/high school	3 (5.00)	6 (10.00)		
College/undergraduate	14 (23.33)	9 (15.00)		
Medical burden (CNY)	3300 ± 2700	3000 ± 1600	-0.865	0.389
Annual household income (CNY)	45200 ± 32800	38500 ± 29200	-1.178	0.241

The variable data adopts *t*-test, and the attribute data adopts χ^2 test, n = 60. There was no significant difference between the intervention group and the control group ($P > 0.05$).

perceive the attitudes and behaviors of others in a situation, and how their performance respond to the patient's behaviors. Patients are encouraged to be friendly to group members (behavioral activation: Greeting, asking for help, *etc*.) and then to observe if the group members are interested in them. Friendly feedback from others encourages patients to be more positive in their interpersonal interactions. When prejudicial attributions and negative self-evaluations such as "I can't do it", "I'm useless", "No one wants to help me", "I'm not the same as others" occur, self-focus is enhanced through family companionship, empathic psychological support, imitative learning among group members, focusing on solving difficult problems, improving self-awareness and insight, and strengthening social skills training. Through positive and effective communication, expressing one's real emotional needs, accessing resource support (family support, peer support and social support), coping with crisis, testing hypotheses in practice and feeling trusted. Recent research has also demonstrated the effectiveness of social skills training in improving negative symptoms[1,12]. Cognitive remediation has a small to moderate beneficial effect on negative symptoms enhancing a positive outcome for cognitive impairment [13,14].

The results showed that combined CBGT and mental health education significantly improved social functioning in patients with schizophrenia, but did not have a significant advantage over single mental health education in improving daily living skills[15]. Related studies found that there were more factors influencing daily living skills, such as executive function (21%), memory and abstract thinking (13.5%), negative symptoms (13%), age of onset and years of education

Table 3 Repeated measures analysis of variance on psychopathology, social function, activities of daily living and psychological condition of family members of patients with schizophrenia

Variables	Control group (n = 60), mean ± SD			Intervention group (n = 60), mean ± SD			Repeated measurement, F-test		
	Before intervention	After intervention	4 wk after intervention	Before intervention	After intervention	4 wk after intervention	Main effect for groups (F, P value, $\eta 2_{partial}$)	Main effect for time points (F, P value, $\eta 2_{partial}$)	Group by time point interaction (F, P value, $\eta 2_{partial}$)
Overall score	101.67 ± 21.48	75.78 ± 19.36	57.90 ± 16.52	97.02 ± 24.40	68.15 ± 18.85	48.72 ± 11.28	F = 5.617, P = 0.019, $\eta 2_{partial}$ = 0.045	F = 344.924, P = 0.000, $\eta 2_{partial}$ = 0.855	F = 0.829, P = 0.439, $\eta 2_{partial}$ = 0.014
Negative factor	35.00 ± 5.42	26.58 ± 5.83	19.77 ± 5.26	32.27 ± 7.48	24.05 ± 6.37	16.45 ± 4.22	F = 9.777, P = 0.002, $\eta 2_{partial}$ = 0.077	F = 452.858, P = 0.000, $\eta 2_{partial}$ = 0.886	F = 0.451, P = 0.638, $\eta 2_{partial}$ = 0.008
Positive factor	14.45 ± 3.50	10.77 ± 3.01	8.07 ± 2.56	13.70 ± 3.53	9.60 ± 2.83	7.40 ± 1.43	F = 3.766, P = 0.055, $\eta 2_{partial}$ = 0.031	F = 243.801, P = 0.000, $\eta 2_{partial}$ = 0.420	F = 0.873, P = 0.420, $\eta 2_{partial}$ = 0.015
Excitatory factor	10.53 ± 3.84	7.45 ± 2.89	5.85 ± 2.28	10.45 ± 3.52	6.85 ± 2.28	5.00 ± 1.29	F = 1.437, P = 0.233, $\eta 2_{partial}$ = 0.012	F = 140.501, P = 0.000, $\eta 2_{partial}$ = 0.451	F = 0.801, P = 0.451, $\eta 2_{partial}$ = 0.014
Cognitive factor	22.75 ± 4.72	17.38 ± 4.35	13.45 ± 3.72	21.37 ± 5.61	15.37 ± 4.25	11.23 ± 2.83	F = 7.751, P = 0.006, $\eta 2_{partial}$ = 0.062	F = 275.171, P = 0.000, $\eta 2_{partial}$ = 0.825	F = 0.505, P = 0.605, $\eta 2_{partial}$ = 0.009
Anxiety and depression factor	18.82 ± 6.04	13.70 ± 5.36	11.15 ± 4.31	18.45 ± 6.61	12.07 ± 4.82	8.77 ± 3.00	F = 3.409, P = 0.067, $\eta 2_{partial}$ = 0.028	F = 153.796, P = 0.000, $\eta 2_{partial}$ = 0.724	F = 2.130, P = 0.123, $\eta 2_{partial}$ = 0.035
SDSS score	12.98 ± 3.55	11.1 ± 3.50	8.72 ± 3.82	12.82 ± 3.03	9.48 ± 3.23	6.18 ± 3.40	F = 5.798, P = 0.018, $\eta 2_{partial}$ = 0.047	F = 593.573, P = 0.000, $\eta 2_{partial}$ = 0.910	F = 30.062, P = 0.000, $\eta 2_{partial}$ = 0.339
ADL score	20.13 ± 8.49	16.78 ± 3.95	16.25 ± 3.23	21.05 ± 8.94	16.90 ± 4.00	16.23 ± 2.99	F = 0.134, P = 0.715, $\eta 2_{partial}$ = 0.001	F = 28.065, P = 0.000, $\eta 2_{partial}$ = 0.324	F = 0.323, P = 0.724, $\eta 2_{partial}$ = 0.005

Repeated measurement ANOVA, n = 60. PANSS: Positive and negative syndrome scale; SDSS: Social function deficiency screening scale; ADL: Activities of daily living.

(8%)[16]. This shows that the improvement in cognitive function facilitates the improvement of patient independent living in their communities and issue management in their daily lives. We also saw that the short duration of the intervention and the influence of other related factors, among others, suggest that further research is needed to reveal the effect of CBGT on other factors related to the abilities of schizophrenia patients in their everyday lives.

Furthermore, the results suggest that CBGT combined with mental health education did not have a significant impact on medication adherence in schizophrenia patients, and only slightly increased the proportion of patients who were fully adherent. We can see that outpatients' medication adherence (duration of medication) was more stable under family medication supervision, but we speculate that this may be related to a number of factors influencing adherence, including severity of illness, level of awareness of illness, duration and dosage of medication, family factors, environmental factors, and doctor-patient relationship[17-19]. In future studies, we may need to optimize adherence assessment criteria and will further explore the correlation between adherence and other factors.

We know that treatment with CBGT can have a positive impact on the pathophysiology and cognitive control networks in functional areas of the brain such as the anterior cingulate cortex, dorsolateral striatum, dorsolateral prefrontal cortex, amygdala, basal ganglia, and thalamus, and this evidence provides the basis for a neurobiological brain mechanism for CBGT treatment to relieve negative symptoms and cognitive impairments[20-29]. This study has demonstrated that

Table 4 Medication compliance in the two groups using χ^2 test, *n* (%)

	Pre-intervention compliance		Post-intervention compliance		Compliance at 4 wk after intervention	
	Complete compliance	Partial compliance	Complete compliance	Partial compliance	Complete compliance	Partial compliance
Control group (n = 60)	49 (81.67)	11 (18.33)	48 (80.00)	12 (20.00)	53 (88.33)	7 (11.67)
Intervention group (n = 60)	52 (86.67)	8 (13.33)	50 (83.33)	10 (16.67)	55 (91.67)	5 (8.33)
χ^2	0.563		0.223		0.370	
P value	0.453		0.637		0.543	

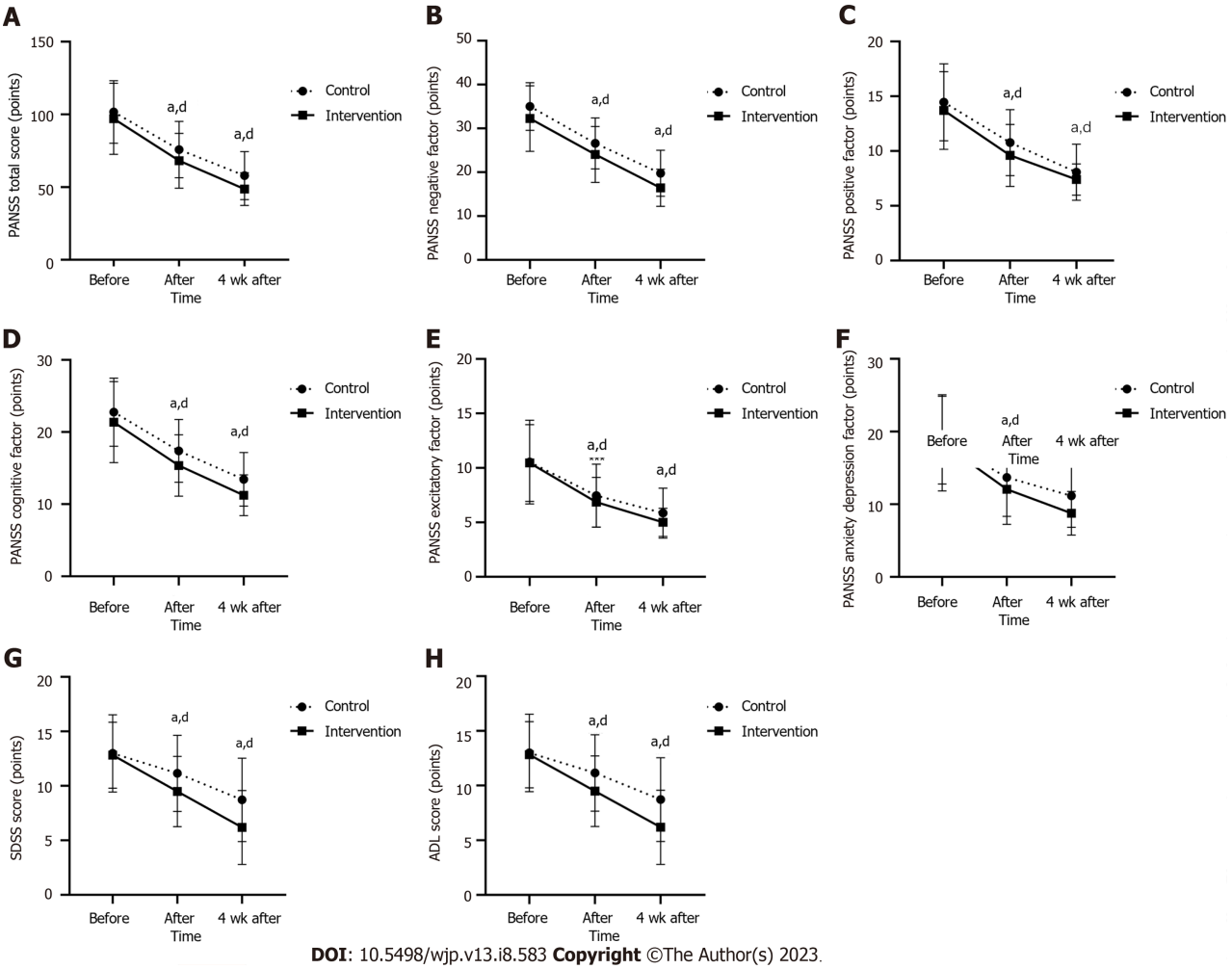

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Figure 1 Difference between groups over time using repeated measurement ANOVA. A: Positive and negative symptom scale (PANSS) total score; B: PANSS negative symptom factor score; C: PANSS positive symptom factor score; D: PANSS cognitive factor score; E: PANSS excitatory factor score; F: PANSS anxiety and depression factor score; G: Social function deficiency screening scale score; H: Activity of daily living ADL. [a]P < 0.001 (differences between within-subjects over time using pairwise t test); [d]P < 0.001 (differences between within-subjects over time using pairwise t test). PANSS: Positive and negative syndrome scale; SDSS: Social function deficiency screening scale; ADL: Activity of daily living.

CBGT combined with mental health education intervention improved social functioning, enhanced work drive, interpersonal interactions and cognitive functioning (verbal communication), and reduced positive symptoms, and negative symptoms better than single mental health education in community-rehabilitated schizophrenia patients.

There are some limitations to this study. Firstly, the sample size of this study is relatively small and our findings are preliminary and need to be further validated in an expanded patient sample. Secondly, although the PANSS scale is a screening tool to assess psychopathological symptoms, it cannot further assess quantitative cognitive functions such as executive function, reasoning, attention, verbal-visual learning, and working memory. In future studies, we should select corresponding assessment tools to test the relationship between research CBGT and cognitive impairment. Thirdly, only

the duration of medication was considered when evaluating medication adherence. We need to include other relevant factors (such as disease severity, medication duration and dosing) as measurements to effectively evaluate adherence in patients taking medication regularly in outpatient clinics. Fourthly, this study is a cross-sectional study and suffers from the general limitation of clinician and patient blinding settings that cannot be overcome by CBGT studies, which may lead to a high risk of bias in the assessment results. Further measurements of cognitive function, duration of illness, dosing of medication and other relevant factors are needed in the future to help support the clinical evidence.

CONCLUSION

In conclusion, our data support the view that CBGT combined with mental health education improves clinical symptoms and psychosocial rehabilitation outcomes in people with schizophrenia in the community. Good medication adherence lays the foundation for psychosocial recovery. The degree of family involvement in patient medication supervision has a significant impact on patient psychiatric recovery. Support systems such as family support, peer support and social support are important positive factors for community rehabilitation. Patients can gain social experiences in group-based activity exchanges, gain emotional support and recognition through mutual imitation and learning exchanges, enhance resilience and thus rebuild rational beliefs and strategies, and it also provides some guidance on the development of community rehabilitation models in patients with mental illness.

ARTICLE HIGHLIGHTS

Research background

Cognitive behavioral therapy is an evidence-based adjunctive intervention for schizophrenia and has shown benefits.

Research motivation

Whether the combination therapy of cognitive behavioral group therapy (CBGT) and mental health education shows superior benefits to mental health education alone in the management of schizophrenia?

Research objectives

This study aimed to compare the efficacy of CBGT combined with mental health single mental health education and mental health education alone for schizophrenia.

Research methods

A total of 120 patients with schizophrenia were enrolled and allocated to an intervention group (n = 60) and a control group (n = 60). Patients in the intervention group received CBGT therapy which was added as an adjunctive intervention to antipsychotics and mental health education. Patients in the control group only received antipsychotic drugs and mental health. The cycle of treatment is 8 wk. After a follow-up of four weeks, score for positive and negative symptom scale, social function, activities of daily living and medication compliance were measured.

Research results

It showed that 8 wk of CBGT combined with mental health education significantly alleviated symptoms and cognitive dysfunction and improved social functioning although it did not have a significant impact on medication adherence in patients with schizophrenia after 4 wk of follow-up.

Research conclusions

The results of this study indicate that the combination therapy of CBGT and mental health education is a promising addition to antipsychotics.

Research perspectives

To attain robust results, further large-scale studies should be conducted with the measurements of cognitive function, duration of illness, dosing of medication and other relevant factors are considered to support the clinical evidence.

FOOTNOTES

Author contributions: Chen XL and Deng XT were responsible for study design and data analysis; Sun FG was responsible for data acquirement and mental health education; Chen XL was responsible for cognitive behavioral group therapy; Chen XL and Huang QJ drafted the manuscript and revised it critically; and all the authors critically reviewed the manuscript and gave final approval for its publication.

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SCIENTOMETRICS

Global research trends and mapping knowledge structure of depression in dialysis patients

Samah W Al-Jabi

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Abstract

BACKGROUND

Depression is one of the most common and important psychological issues faced by dialysis patients. It can make it more difficult for them to adhere to their treatment regimen, which, in turn, can worsen their physical symptoms and lead to poorer health outcomes.

AIM

To examine the evolution and growth of publications related to dialysis and depression. The objectives were to identify the number of publications, the top active countries, the contributed institutions, funding agencies and journals, as well as to perform citation and research theme analysis.

METHODS

The search was conducted using the Scopus database for publications related to dialysis and depression between 1970 and 2022. Subsequently, bibliometric analysis was carried out on the data obtained using VOSviewer software, version 1.6.9. This analysis included visualization analysis, co-occurrence analysis and examination of publication trends in dialysis and depression.

RESULTS

We identified 800 publications that met the search criteria. The number of publications related to dialysis and depression has increased significantly in the past two decades. The USA led the way with 144 publications, which is 18% of all publications on this topic. Turkey came second with 88 publications (11%), followed by China with 55 publications (6.88%) and Iran with 52 publications (6.5%). Analysis of the research theme identified three main clusters related to gender differences in prevalence, identification of depression as a risk factor, and effective interventions to relieve depression. Future research direction analysis shows a shift toward effective interventions to relieve depression in dialysis patients.

CONCLUSION
This study provides a comprehensive overview of growth, trends and research themes related to dialysis and depression that could help researchers identify gaps in the literature and develop future research.

Key Words: Dialysis; Depression; Bibliometric; Hot issues; Scopus

Core tip: Depression is a prevalent psychological problem among dialysis patients, and it can negatively impact their adherence to treatment and health outcomes. A total of 800 publications were identified through a bibliometric analysis of dialysis- and depression-related publications between 1970 and 2022. In the last two decades, there has been a significant increase in the number of publications, and the USA led the way. The identified research themes were gender differences in depression prevalence, the identification of depression as a risk factor, and effective interventions to treat depression. Effective interventions to ameliorate depression in dialysis patients will be the focus of future research endeavors.

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INTRODUCTION

Dialysis is life-sustaining management for patients who have lost renal function due to kidney failure[1,2]. Although it can be an effective treatment for many, it is a complex and demanding procedure that can have significant effects on patients' physical, mental and emotional well-being[3,4]. Depression is a prevalent mental health issue that dialysis users regularly experience[5]. A sensation of despair, hopelessness and helplessness characterizes this syndrome[6]. The stress and ambiguity of treating a chronic illness such as renal failure, as well as the other lifestyle changes that occur alongside dialysis therapy, such as changes to one's diet and daily routine, may all contribute to the onset of depression[7].

According to one study, depression can dramatically affect dialysis patients' quality of life[8]. This can result in psychological and physical symptoms such as weariness, sleeplessness, lack of appetite and loss of interest in previously rewarding activities[9]. Furthermore, depression might make it more difficult for patients to stick to their treatment plan, exacerbating physical symptoms and resulting in poorer health outcomes[10-12]. Several studies have been conducted in recent years to investigate the link between dialysis and depression[13-17]. According to several studies[18-21], depression is more prevalent among dialysis patients than among the general population. Additionally, another study suggests that certain characteristics, such as dialysis duration or changes in dialysis, may increase the incidence of depression[22,23].

A research methodology that studies the organization of academic literature to indicate research trends, patterns and areas of competence is bibliometric and visualization mapping. We may acquire a clearer grasp of the field's structure and geography, identify gaps in knowledge and highlight key contributions by using this methodology to study dialysis and depression[24-27]. This paper reviews the current state of dialysis and depression research, identifies the most influential research publications and institutions and outlines prospective future research directions. It also seeks to provide a complete overview of dialysis and depression research, highlight major research trends and knowledge gaps, and make recommendations for future research. In addition, this study can help researchers to identify voids in the current literature and guide future efforts to advance our understanding of the complex relationship between dialysis and depression.

MATERIALS AND METHODS

Data acquisition

Scopus was chosen to retrieve the publication sources. To avoid potential bias from the daily updates in Scopus, the documents for this study were retrieved and saved on April 12, 2023. The majority of bibliometric studies use Scopus[28-32] and Web of Knowledge[33-35]. Scopus is regarded as the most advantageous database for such analyses due to its numerous benefits[36-40]. Its bibliometric indicators are simple and straightforward. In addition, Scopus includes publications from Medline. Scopus has a number of benefits over Google Scholar and Web of Science. It has a more comprehensive database for bibliometric analysis and covers social sciences and humanities. Its unique characteristics, such as author identification, improve the tracking and evaluation of academics' influence on a particular topic. By offering filtering and sorting options, Scopus facilitates the discovery of relevant research.

Search strategy

A detailed review of the systematic and meta-analysis research on the topic was undertaken to establish the search approach, as referenced in the sources[18-21]. Scopus Engine was used to integrate relevant words connected with dialysis and depression, including Medical Subject Headings from PubMed and prior systematic reviews and meta-analyses. There were four steps in the research strategy. (1) The initial step involved using specific terms and phrases related to dialysis to conduct a title search, which included the following. TITLE ("artificial kidney therapy") OR TITLE (*dialysis*) OR TITLE (extracorporeal therapy) OR TITLE (Hemofiltration) OR TITLE (hemodiafiltration) OR TITLE (hemoperfusion) OR TITLE ("continuous renal replacement therapy"). (2) The second step used specific terms and phrases that are related to depression to conduct a title search that included the following: (TITLE (depress*) OR TITLE (dysthym*) OR TITLE ("seasonal affective") OR TITLE ("bipolar disorder") OR TITLE ("mood disorder*") OR TITLE ("affective disorder")). (3) In the third step, the first two steps were merged and filtered by implementing exclusions and limitations. The search was conducted in Scopus, including articles published up to December 31, 2022, without language restrictions. The research methodology employed the wildcard symbol (*) and quotation marks ("") to refine the search for particular terms or phrases. Errata and retracted documents were excluded from the analysis. (4) The search query resulted was as follows: ((TITLE(depress*) OR TITLE("seasonal affective") OR TITLE(dysthym*) OR TITLE("affective disorder") OR TITLE("mood disorder*") OR TITLE("bipolar disorder")) AND ((TITLE ("Artificial kidney therapy") OR TITLE (*dialysis*) OR TITLE (Extracorporeal therapy) OR TITLE (Hemofiltration) OR TITLE (Hemodiafiltration) OR TITLE (Hemoperfusion) OR TITLE ("Continuous renal replacement therapy")) AND PUBYEAR < 2023)) AND (EXCLUDE (DOCTYPE,"er")).

The search strategy used involved searching for the title using specific keywords rather than searching for both the title and the abstract simultaneously. This approach is considered reliable because it yields minimal false-positive results[41-45]. In contrast, searching for both titles and abstracts may result in a large number of false positives, as the studies' primary focus is on topics other than dialysis and depression.

Validation of the search strategy

The author has taken several steps to ensure the accuracy and reliability of the search query. Firstly, the author improved the query to eliminate false positives. Then, we examined the top 50 most cited papers for relevance to the search subject. Two bibliometric specialists evaluated the title and abstract of these papers and ensured that there were no false positives. The search query was declared complete once it was completed. To confirm that there were no false negatives, the author ran a correlation test between the collected data and the real findings of the field's 20 most active researchers. This test found a strong correlation (r = 0.960) and a significant result (P = 0.001), showing that the search query was precise. This validation method has already been employed in bibliometric studies[46-48]. The rigorous approach and cooperation of two bibliometric specialists enhanced the findings' trustworthiness, and the correlation test gave additional support.

Indices of research productivity

The data collected served as the basis for generating the following information[32,49,50]: (1) Comprehensive analysis and trends of global contributions in publications regarding dialysis and depression from 1970 to 2022; (2) examination of scientific research productivity and collaboration patterns by country; (3) evaluation of research productivity among the most prolific institutions; (4) identification of funding agencies involved; (5) determination of the journals in which international researchers published their work; and (6) assessment of the citations received by these publications.

Bibliometric indicators were utilized to rank the data using the standard competition ranking methodology. Only the top 10 rankings were considered and if two ranking numbers were the same, a gap was left in the subsequent ranking numbers (*e.g.*, 1, 2, 3, 3 and 5)[51]. The quality of research productivity was assessed using the h-index, which represents the number of articles (h) that have received at least h citations[52]. For example, if a researcher has 50 published journal articles, they would have an h-index of 10 if 10 of those papers have received at least 10 citations each and the remaining 40 papers have fewer than 10 citations each. The impact factor was used as an indicator to gauge the importance of the journals, evaluated using the Journal Citation Report (Clarivate Analytics) for the year 2022.

The presented Impact Index per Article refers to the top 10 highly cited papers obtained from the Reference Citation Analysis (RCA) database, which is an open, multidisciplinary citation analysis database owned by Baishideng Publishing Group, located in Pleasanton, CA, USA[53-55].

Visualization analysis

VOSviewer software (version 1.6.9, Leiden University, Leiden, The Netherlands) was used to create network maps depicting the relationships between terms identified in titles or abstracts, as well as cross-national cooperation[56-58]. VOSviewer allows the establishment of knowledge networks by utilizing co-occurrence analysis, which provides a scientific foundation for projecting future research hotspots and following the advancement of various research disciplines[56-58]. By clustering terms based on their co-occurrence, VOSviewer assigns a unique color to each cluster, which can be used to identify and analyze research hotspots more effectively. This approach allows for the visualization and detection of developing trends. Terms are represented as nodes and the associations between them are depicted as lines or links. The thickness of the lines represents the strength of the association between the terms.

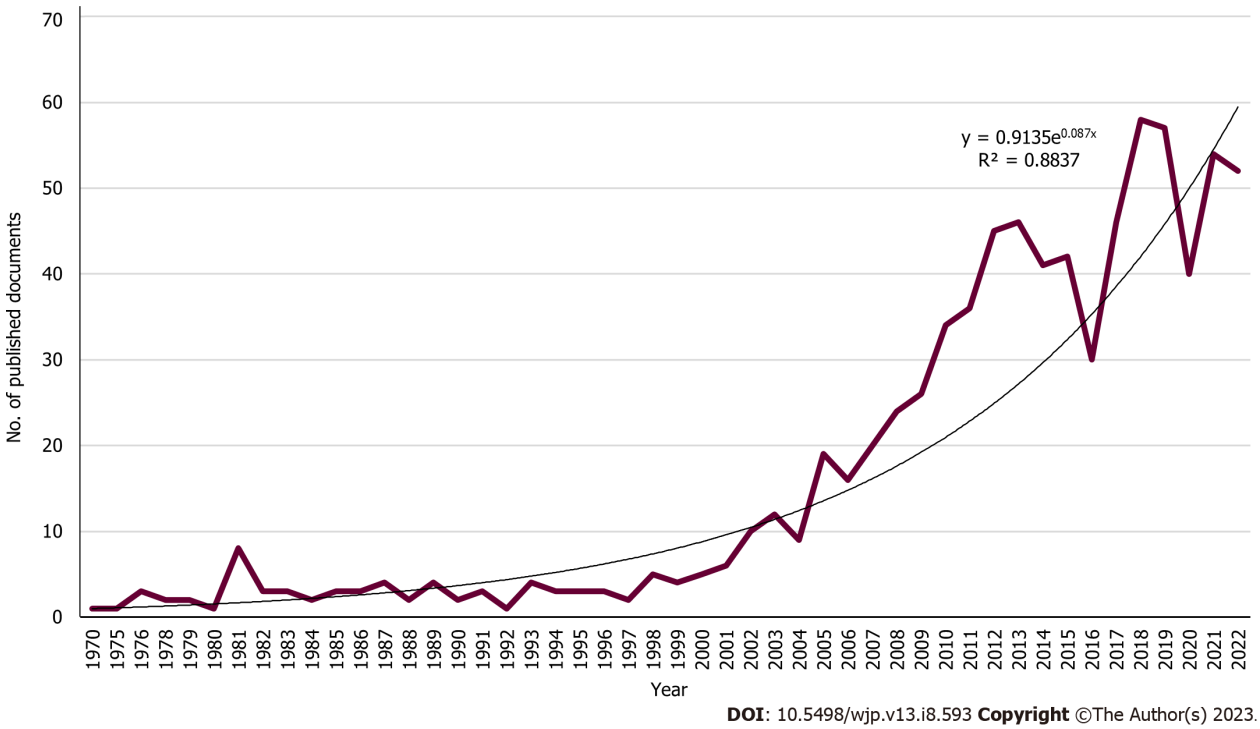

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Figure 1 Number of articles analyzed in a bibliometric study on global dialysis and depression-related publications between 1970 and 2022.

RESULTS

Evolution and growth of publications

We identified 800 publications that met the search criteria between 1970 and 2022. Of these, 707 (88.38%) were original research articles, 33 (4.13%) were reviews, 29 (3.63%) were letters to the editor and 31 (3.88%) fell under other categories, such as notes or editorials. The number of publications related to dialysis and depression has increased significantly in the last two decades, with fewer than three articles published annually before 2002. However, since 2013, the number of publications related to dialysis and depression has grown much more rapidly, with more than 46 articles published annually (Figure 1).

Top active countries

In fact, 93 countries have contributed to the literature on dialysis and depression, according to Scopus. The USA led the way with 144 publications, which was 18% of all publications on this topic; Turkey came second with 88 publications (11%), followed by China with 55 publications (6.88%) and Iran with 52 publications (6.5%) (Table 1). Figure 2 depicts the countries with > 10 publications on dialysis and depression, highlighting their collaborative network. The larger the circle, the more publications from that country will be published; and the thicker the line, the stronger the collaboration. The width and number of lines on the map reflect the intensity and degree of interaction between the countries represented. We focused on five VOSviewer clusters to assess their centrality and linkages with other countries. The data are based on a study of 21 countries (as seen in Figure 2), with the USA and Turkey contributing the most publications to the purple cluster.

Contributing institutions

According to Table 2, the top 10 institutions in the study generated a total of 89 publications, representing 11.13% of all the analyzed publications. On examining the papers related to dialysis and depression, the Leids Universitair Medisch Centrum came out on top, producing 18 publications, followed by the Onze Lieve Vrouwe Gasthuis with 14 publications, the VA Medical Center with 13 publications and the University of Hertfordshire with 13 publications.

Contributed funding agencies

Table 3 shows the leading funding agencies according to their production. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institutes of Health (NIH) and the Japan Society for the Promotion of Science (JSPS) emerged as the most productive funding agencies, the NIDDK leading with 26 (3.25%), followed by the NIH with 15 (1.88%) and the JSPS with 11 (1.38%).

Table 1 Top 10 countries ranked by article output on dialysis and depression from 1970 to 2022

Ranking	Country	No. of documents	%
1	USA	144	18.00
2	Turkey	88	11.00
3	China	55	6.88
4	Iran	52	6.50
5	Brazil	42	5.25
5	United Kingdom	42	5.25
7	Japan	38	4.75
8	South Korea	37	4.63
9	Taiwan	35	4.38
10	Canada	25	3.13

Table 2 Top 10 institutions with the highest frequency of article publications on dialysis and depression worldwide, ranked by productivity

Ranking	Institute	Country	No. of documents	%
1	Leids Universitair Medisch Centrum	Netherlands	18	2.25
2	Onze Lieve Vrouwe Gasthuis	Netherlands	14	1.75
3	VA Medical Center	USA	13	1.63
3	University of Hertfordshire	UK	13	1.63
5	Amsterdam UMC	Netherlands	12	1.50
5	The Lister Hospital	UK	12	1.50
5	The University of Jordan	Jordan	12	1.50
8	University of Toronto	Canada	11	1.38
9	The George Washington University	USA	10	1.25
9	King's College London	UK	10	1.25
9	Başkent Üniversitesi	Turkey	10	1.25

Contributing journals

Table 4 lists the top 10 journals ranked by number of publications, which together make up approximately 21.16% of all publications. *International Urology and Nephrology* had the highest number of publications, with 24, followed by *Renal Failure* with 20 publications and *Kidney International* with 16 publications.

Citation analysis

In total, the top 10 articles received 2715 citations, with an average of 271.5 citations per article. The number of citations ranged from 206 to 446[59-68]. Table 5 displays the publications that garnered > 205 citations and were among the top 10. The impact index per article of the 10 most cited articles ranged from 4.9 to 16.6 (Table 5).

Research themes in the literature on dialysis and depression

Figure 3 presents the most commonly used terms in the titles and abstracts of the articles related to dialysis and depression. The size of the circle indicates the frequency of the term, while the distance between two circles or terms indicates their co-occurrence. The terms are grouped based on their close relationship and are represented by different colors. Cluster analysis identified three main clusters, displayed in green, blue and red. The green cluster relates to "gender differences in the prevalence of depression and anxiety among dialysis patients", the red cluster to "identification of depression as a potential risk factor for poor outcomes in dialysis patients", and the blue cluster to "effective interventions to alleviate depression in dialysis patients". The blue cluster was significantly associated with terms from other clusters. Overall, the three clusters are presented in Figure 3.

Table 3 The top ten funding agencies that have the most publications in research related to dialysis and depression from 1970 to 2022

Ranking	Funding agencies	Country	No. of publication	%
1	National Institute of Diabetes and Digestive and Kidney Diseases	USA	26	3.25
2	National Institutes of Health	USA	15	1.88
3	Japan Society for the Promotion of Science	Japan	11	1.38
4	National Center for Advancing Translational Sciences	USA	9	1.13
5	National Heart, Lung, and Blood Institute	USA	8	1.00
5	National Natural Science Foundation of China	China	8	1.00
5	Nierstichting	Netherlands	8	1.00
8	National Institute for Health Research	UK	7	0.88
9	Conselho Nacional de Desenvolvimento Científico e Tecnológico	Brazil	5	0.63
9	National Institute of Mental Health	USA	5	0.63
9	US Department of Veterans Affairs	USA	5	0.63

Table 4 The top 10 journals in research related to dialysis and depression

Ranking	Journal/source title	No. of documents	%	IF[1]
1	*International Urology and Nephrology*	24	3.0	2.266
2	*Renal Failure*	20	2.50	3.222
3	*Kidney International*	16	2.0	18.988
4	*Clinical Journal of the American Society of Nephrology*	15	1.88	10.614
4	*General Hospital Psychiatry*	15	1.88	7.587
4	*Journal of Psychosomatic Research*	15	1.88	4.62
4	*Nephrology Dialysis Transplantation*	15	1.88	7.186
8	*American Journal of Kidney Diseases*	14	1.75	11.072
9	*Hemodialysis International*	13	1.63	1.543
10	*BMC Nephrology*	11	1.38	2.585
10	*Clinical Nephrology*	11	1.38	1.243

[1]Journal Citation Reports (Clarivate, 2022).
IF: Impact factor.

Future research direction analysis

In Figure 4, VOSviewer assigned distinct colors to each term based on the frequency of its appearance in all retrieved publications. Blue was assigned to the terms that first emerged in the literature, whereas yellow was assigned to those that were recently discovered. Before 2014, research in this field focused on the connection between "gender differences in the prevalence of depression and anxiety among dialysis patients" and "identification of depression as a possible risk factor for poor outcomes in dialysis patients". However, the latest research trends, discovered after 2014, revolved around "effective interventions to alleviate depression in dialysis patients".

DISCUSSION

Bibliometric analysis is a useful method for evaluating the global research landscape of a specific field. This work's analysis provides insights into the research on depression and dialysis, demonstrating that it has been a topic of interest to scientists worldwide. The prominence of the USA, Turkey and China suggests that these nations may have made distinctive contributions to the discipline. This analysis also yields the identification of notable contributors, such as institutions, journals and funding agencies. These contributors may serve as valuable resources for future researchers seeking collaboration or funding. Identified trends and concentrations in the field of research can help to guide future investigations and inform policy decisions regarding depression and dialysis. Forecasting future developments is also

Table 5 The ten most cited publications in research related to dialysis and depression from 1970 to 2022

Ranking	Ref.	Title	Source title	Cited by	Impact Index Per Article[1]
1	Kimmel *et al*[63], 2000	Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients	*Kidney International*	446	15.7
2	Lopes *et al*[66], 2002	Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe	*Kidney International*	434	16.6
3	Watnick *et al*[67], 2003	The prevalence and treatment of depression among patients starting dialysis	*American Journal of Kidney Diseases*	258	11.1
4	Hedayati *et al*[61], 2006	The predictive value of self-report scales compared with physician diagnosis of depression in hemodialysis patients	*Kidney International*	243	12.1
5	Kimmel *et al*[64], 1993	Survival in hemodialysis patients: The role of depression	*Journal of the American Society of Nephrology*	235	6.7
5	Lopes *et al*[65], 2004	Screening for depression in hemodialysis patients: associations with diagnosis, treatment, and outcomes in the DOPPS.	*Kidney international*	233	10.3
7	Watnick *et al*[68], 2005	Validation of 2 depression screening tools in dialysis patients	*American Journal of Kidney Diseases*	231	11.3
8	Craven *et al*[59], 1988	The Beck Depression Inventory as a screening device for major depression in renal dialysis patients.	*International journal of psychiatry in medicine*	220	4.9
9	Kimmel and Peterson [62], 2005	Depression in end-stage renal disease patients treated with hemodialysis: Tools, correlates, outcomes, and needs	*Seminars in Dialysis*	209	10.8
10	Finkelstein and Finkelstein[60], 2000	Depression in chronic dialysis patients: Assessment and treatment	*Nephrology Dialysis Transplantation*	206	6.6

[1]The Impact Index Per Article is presented based on *Reference Citation Analysis* [Source: Baishideng Publishing Group Inc (Pleasanton, CA 94566, United States)].

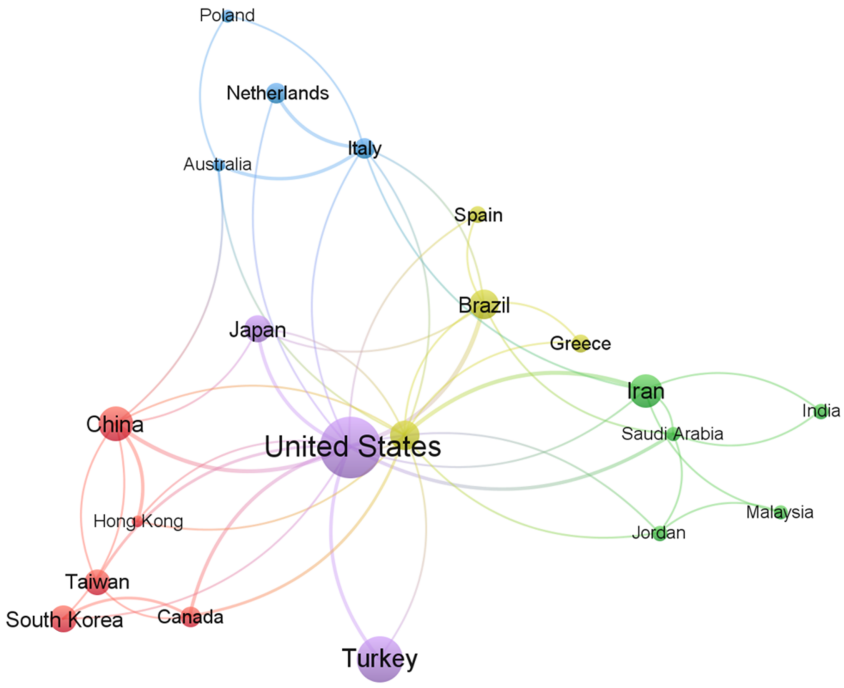

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Figure 2 Visualization of the network of international research collaboration on dialysis and depression among 21 countries with a minimum research output of 10 documents. VOSviewer software version 1.6.19 was used to generate the map.

beneficial for researchers, clinicians and policymakers who wish to anticipate future requirements and plan accordingly.

This study reveals that the amount of research evaluating the literature on dialysis and depression has increased consistently over the past two decades. In the foreseeable future, the amount of research into the connection between

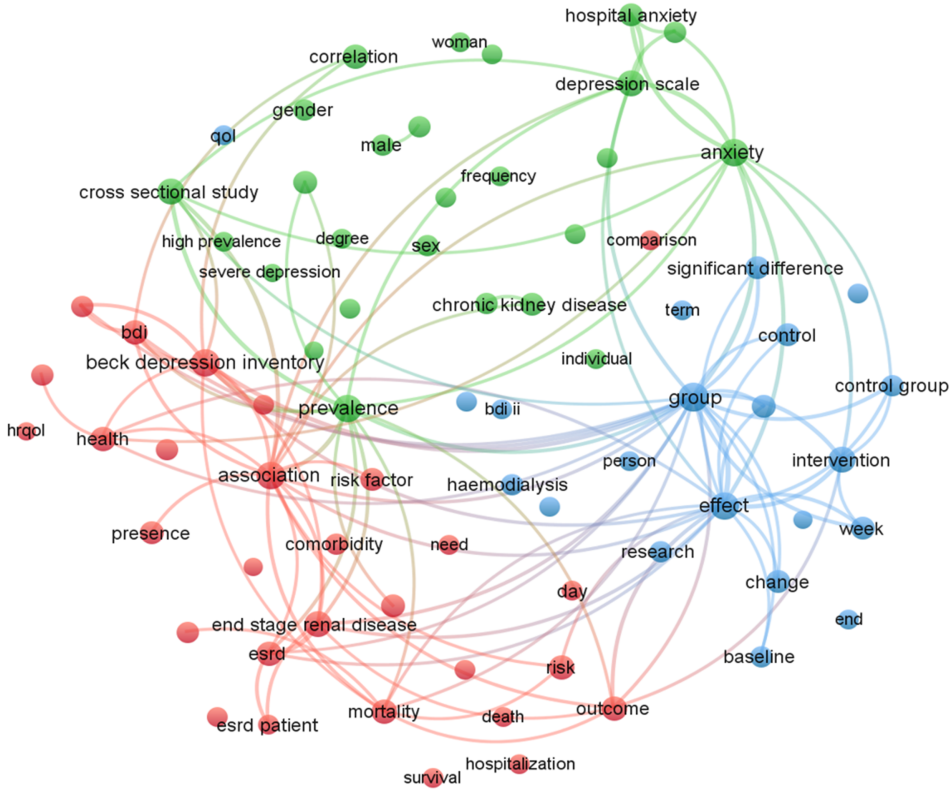

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Figure 3 Map visualizing the network analysis of terms found in titles and abstracts, with a minimum frequency of ten or more. Terms are represented as nodes, and the associations between them are depicted as lines or links. The thickness of the lines represents the strength of the association between the terms. VOSviewer software version 1.6.19 was used to generate the map.

dialysis and depression is likely to increase. This is due to the increasing prevalence of chronic kidney disease (CKD) and the fact that depression is a common comorbidity among patients with CKD, especially those who require dialysis[69,70]. Furthermore, there is growing awareness among healthcare professionals of the impact that depression can have on the overall health and well-being of dialysis patients, as well as a greater emphasis on addressing mental health issues as part of comprehensive care[71,72]. As a result, it is reasonable to anticipate that research on this subject will continue to grow in the coming years.

Research studies to identify nations with a significant presence in a specific research discipline. In this case, the USA was determined to have the most influential research on depression and dialysis. This conclusion was likely reached by analyzing the number of publications and citations in these disciplines from various countries. It is not uncommon for countries to excel in particular areas of research while lagging behind in others[73-76]. Variables such as financial resources, government support, academic infrastructure, and cultural attitudes toward research contribute to scientific productivity. Countries such as Turkey, Iran and Brazil may have devoted more resources to depression and dialysis research, resulting in an increase in the number of publications. Additionally, these countries may have research questions or perspectives that have not been investigated as extensively in other regions. Notably, the connection between economic development and scientific productivity is intricate. Although it is true that countries with larger economies typically have more resources for research, there are numerous instances in which smaller or developing countries make significant scientific contributions. However, it is essential to note that research output does not necessarily equate to quality or influence. Other factors, such as funding, collaboration, and the caliber of research institutions, can also affect a country's research influence[77]. It is also possible that other countries conduct high-quality research in these fields but are not recognized due to language barriers or lack of visibility[78].

The main themes of a research paper are usually reflected in the title and abstracts. When the terms depression and dialysis occur together frequently in a research field, it indicates current trends and progress in that area. Based on this cooccurrence, research on depression and dialysis can be categorized into three aspects: (1) "Prevalence of depression and anxiety among dialysis patients and gender differences"; (2) "Identification of depression as a potential risk factor for poor outcomes in dialysis patients"; and (3) "Effective interventions for alleviating depression in dialysis patients".

The prevalence of depression and anxiety among dialysis patients, as well as gender differences, was one of the most important aspects of the study. There are gender differences in the prevalence and presentation of depression and anxiety in this population[79,80]. According to previous studies, women on dialysis are more likely to experience depression and anxiety than men[79-81]. Several factors, including fluctuations in hormones, social roles and cultural norms, might contribute to this[4,82].

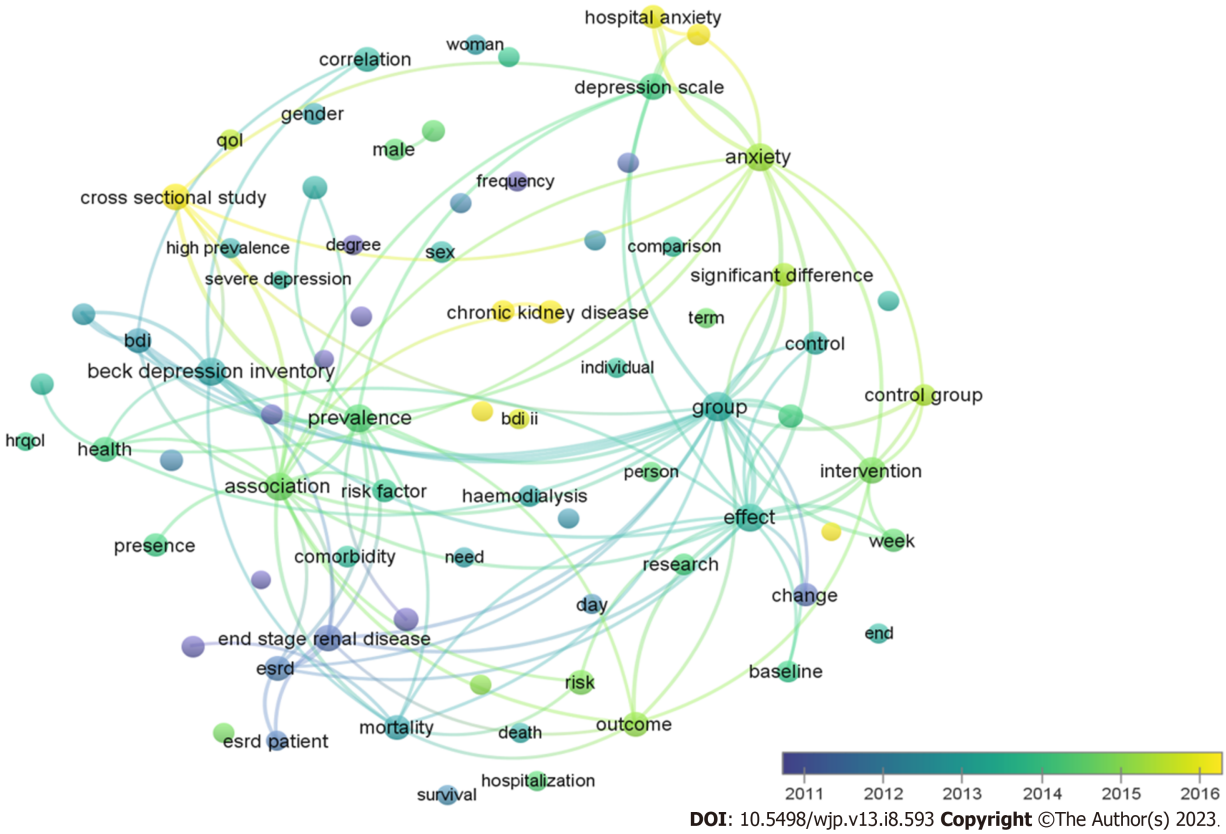

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Figure 4 Map of a network visualization analysis of terms in titles and abstracts based on their frequency of appearance. Blue indicates earlier occurrences of the terms, whereas yellow indicates later occurrences. VOSviewer software version 1.6.19 was utilized to create the map.

The second hot topic was the "identification of depression as a potential risk factor for poor outcomes in dialysis patients". According to previous findings, depression in hemodynamic patients is associated with a decline in the quality of life, an increase in mortality and an increase in healthcare costs[11,83-86]. Depression may also be linked to poor adherence to medicine and diet plans, a higher number of hospitalizations and a lack of social support[87]. Healthcare practitioners must be aware of the likelihood of depression in hemodynamic patients and perform routine screenings. Antidepressant drugs, psychotherapy and lifestyle changes can all be used to treat depression in patients[88,89]. Correctly diagnosing and treating depression in these patients can improve both their mental and physical health[88].

The third hot topic was "effective therapies to relieve depression in dialysis patients". Enhancing the quality of life and health outcomes of dialysis patients involves the deployment of depression-fighting therapies[90,91]. Various therapies have been found to be useful for lowering depression in dialysis patients experiencing hemodynamic lysis[19,92,93]. One of the most widely utilized therapies is antidepressant medication. Antidepressant medication has been proven in various studies to be beneficial for reducing depressive symptoms in dialysis patients, as well as for improving other aspects of their health, such as sleep quality and pain management[94,95]. Cognitive behavioral therapy (CBT) is a successful treatment for depression in dialysis patients. CBT is a type of therapy that aims to change negative thought and behavior patterns[96-98]. Several studies have indicated that CBT can considerably reduce depressive symptoms and enhance dialysis patients' quality of life[96,97]. In addition to CBT, exercise, music therapy and mindfulness-based therapies have been demonstrated to be helpful for treating depression in patients[92,99,100]. It has been shown that exercise enhances mood and reduces depressive symptoms in dialysis patients, whereas music therapy and mindfulness-based interventions may be helpful in the management of stress and anxiety.

Most research publications that involved dialysis patients before 2014 focused on the prevalence and gender differences of depression and anxiety and the identification of depression as a risk factor for negative outcomes in those patients. However, a marked change in research trends has been undertaken since 2014. The emphasis has shifted to focus on effective interventions that improve depression in dialysis patients. Thus, the research has acknowledged the value of addressing the practical elements in managing depression and improving the well-being of patients undergoing dialysis. The following future directions in this field are based on these findings. Although this issue to explore gender differences in the prevalence of depression and anxiety among patients undergoing dialysis was prevalent before 2014, further research may be needed for a deeper understanding of the factors that contribute to gender differences and their effects on treatment and outcome. Previous research has focused mainly on studying the correlation between depression and adverse outcomes, but it is necessary to continue to evaluate the relationship and understand the underlying mechanism of depression's impact on the well-being of patients treated with dialysis. Recent articles focus primarily on methods to help people with depression. In the future, researchers should study various treatments such as medication therapies and social support to determine the most effective methods for alleviating depression in these patients.

Research is needed to investigate the psychological and social factors causing depression and anxiety in patients who require dialysis. This involves assessing factors such as economic difficulties, stress management strategies, the presence of strong support systems and other relevant factors that can influence the development and deterioration of depression in this particular patient group. It is essential to acknowledge the lasting effects of therapeutic interventions on the mental and overall health of dialysis patients. By conducting long-term studies and follow-up evaluations, we can gain valuable information regarding the long-term efficacy and sustainability of various treatment approaches.

By utilizing bibliometrics, this study took a novel approach to understanding the academic literature on the relationship between dialysis and depression. Researchers could easily identify study participants, focal areas of interest and emerging patterns within this specific domain by utilizing visual analysis. Although these methods were useful in identifying research trends and knowledge gaps, they did have some limitations. Firstly, there was a potential risk of bias in the selection of publications and the inability to capture the full complexity of research topics. This was mainly due to our search being limited to Scopus, which, although comprehensive and reputable for numerous academic fields, might have omitted papers from alternative sources such as PubMed and Web of Science. Secondly, the list of keywords used in the study was derived from previous literature reviews and it is possible that some keywords were omitted, resulting in false-negative findings. Thirdly, as the citation searches were time dependent, older articles were more likely to be cited, which may have influenced the study findings. Fourthly, the scope of the investigation was limited to the search for the title and specific search phrases related to dialysis and depression, which may have led to the omission of relevant articles that used different terms. Lastly, the limitations of the Scopus database resulted in the dispersion of research output from active institutions with multiple Scopus profiles and the omission of funding agency names due to variations in publication naming conventions. Therefore, it is essential to refrain from manipulating or merging the Scopus output and to restrict data analysis to the specified method.

CONCLUSION

This study investigated the growth, trends and research topics associated with depression in dialysis patients. Analysis of 800 documents published between 1970 and 2022 revealed a significant increase in research activity over the past two decades, emphasizing the significance of addressing this common psychological condition in dialysis patients. In addition to the USA as the main contributor, Turkey, China and Iran have also made substantial contributions to the field. The study identifies key research areas and three major clusters of findings: gender differences in depression distribution; depression as a risk factor; and effective depression treatments. These findings contribute to the knowledge concerning gender-specific depression in dialysis patients and the development of effective strategies to improve their mental health. In addition, this report proposes future research directions, given the increasing emphasis on effective treatments for depression in dialysis patients. The study highlighted the growing awareness of the influence of depression on treatment adherence and health outcomes in this population. This study contributed to the advancement of knowledge in its field by indicating the way forward for future research on depression treatments for dialysis patients.

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ARTICLE HIGHLIGHTS

Research background

Depression is a prevalent psychiatric disorder among patients with end-stage renal disease. Hemodialysis patients have a significantly higher occurrence of depression than the general population. Similar to other chronic illnesses and the overall population, research indicates that depression in hemodialysis patients is linked to a diminished quality of life and heightened mortality.

Research motivation

To identify knowledge gaps and guide future research directions, it is crucial to comprehend the present status of research and areas of focus within the domains of depression and hemodialysis.

Research objectives

The objective of the research was to offer a comprehensive analysis of the existing research in the area of depression and hemodialysis through bibliometric analysis.

Research methods

A search was performed in the Scopus database to find publications on the topic of dialysis and depression from 1970 to

2022. The acquired data underwent bibliometric analysis utilizing VOSviewer software version 1.6.9. This analysis encompassed visualization, co-occurrence, and examination of publication patterns in the field of dialysis and depression.

Research results

The number of publications addressing the correlation between dialysis and depression has increased substantially over the past 20 years. Prior to 2002, the yearly publication count was below three. Nonetheless, starting from 2013, there has been a remarkable acceleration in the publication rate, surpassing 46 articles per year, specifically focusing on dialysis and depression.

Research conclusions

Three significant research topics have emerged, focusing on the varying occurrence of depression and anxiety based on gender, recognizing depression as a contributing factor to negative consequences, and assessing the effectiveness of therapies in reducing depression among individuals undergoing dialysis.

Research perspectives

The objective of this study was to determine present patterns and focal points in the domain of dialysis and depression. This will aid in directing future research and updating clinical practices. Through the utilization of bibliometric analysis, the study offers a thorough summary of the literature concerning this subject matter. Consequently, it facilitates researchers and clinicians in keeping abreast of the most recent advancements in the field.

FOOTNOTES

Author contributions: Al-Jabi SW developed the concept for the manuscript, reviewed the literature, formulated research questions, collected the data, conducted analyses and interpreted the data. The author read and approved the final manuscript.

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