RESILIENCE IN CHRONIC DISEASE

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RESILIENCE IN CHRONIC DISEASE

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EDITORIAL
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Editorial: Resilience in Chronic Disease

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Editorial on the Research Topic

Resilience in Chronic Disease

Resilience is usually defined as one's ability to "bounce back" from adversity and is a salient indicator of the quality of life and psychosocial functions of patients facing chronic diseases, for instance, cancer, hypertension, irritable bowel syndrome, and heart failure, etc. (1, 2). Thus, resilience is an important attribute for patients who face the challenge of chronic disease. How patients gain or lose resilience resources during the diagnosis, treatment, and ultimately the survival of chronic disease is attracting increased attention in bio-psycho-social medicine. Interestingly, there exist many different concepts of resilience including physiological, psychological, social, and spiritual resilience, that involve a variety of factors, from behavioral constructs like defense mechanisms, beliefs, and personalities to molecular levels of brain-derived neurotrophic factor, neuropeptide Y, and oxytocin in emotion- and cognition-related brain areas (3, 4). The factors underpinning psychological and social resilience are less established and therefore the primary focus in this collection. However, the construct of resilience has not been established and whether resilience should be defined as a state or trait continues to be debated (5). This collection aims to fill gaps in knowledge regarding the predicted ability of resilience to enhance long-term quality of life and other psychosomatic outcomes in patients with different chronic diseases, which need to be further explored and clarified.

The call for submissions on *Resilience in Chronic Disease* received a great response. The collection consists of 12 studies with a total of over 7,100 participants from different countries. A diversified array of populations including the general population in the COVID-19 pandemic (Büssing et al.), patients with chronic pain (Orakpo et al.), cancer (Tang et al.), irritable bowel disease (Funaba et al.; Luo et al.), cardiovascular disease (Qiu R. et al.), neurocognitive disorders (Wang et al.), renal transplant (Hu et al.), and rheumatoid arthritis (Shen et al.), as well as caregivers for children with chronic illness (Qiu, Xu et al.), patients with liver cancer (Mao et al.), and maintenance hemodialysis (Qiu, Huang et al.), were examined. Findings derived from the current collection echo the existing positive-psychology literature emphasizing the importance of psychological and social resilience in the move forward with chronic disease. Scientists from multi disciplines have contributed to this collection, providing contributions that raise awareness, educate, and reduce the impact of different chronic diseases on patients and their caregivers. However, several limitations should be emphasized here. First, most articles used observational designs (i.e., Büssing et al.; Tang et al.; Luo et al.; Qiu, Huang et al., etc.), describing resilience and its associations with other aspects of the psychological, social, and physical well-being of patients with chronic disease. Our specific aim was first, to recognize distinct resilience trajectories during diagnosis, treatment, and survivorship throughout the course of chronic disease, which was not achieved in the current collection (6, 7). Second, articles about resilience theory and instrument development are limited, and more future research should be undertaken to develop new resilience theories and instruments for the cultural

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and developmental levels of measuring the psychological and social aspects of resilience, which can help address debates about resilience construction (8–10). Third, the predicted ability of resilience to enhance the long-term quality of life and other psycho-somatic outcomes in patients with different chronic diseases is not fully explained (11). Prevention-oriented studies investigating how resilience mitigates the effect of chronic disease on patients' health in different phases (i.e., first diagnosis, remission, relapse) should be further explored. Fourth, in the move forward with resilience research in chronic disease, investigating the efficacy, sustainability and implementation challenges of resilience programs targeting patients with chronic disease and their caregivers should be the next step in furthering knowledge [Seiler et al.; (12–15)].

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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CASE REPORT
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Case Report: Virtual Reality Neurofeedback Therapy as a Novel Modality for Sustained Analgesia in Centralized Pain Syndromes

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Neurofeedback (NFB) Therapy is a form of biofeedback, using the electroencephalogram (EEG) that has been in use since the 1970s, serving as a non-pharmacological intervention for epilepsy and psychiatric conditions such as anxiety, depression, insomnia, PTSD, post-concussive syndrome, and now, centralized pain. Chronic pain can increase neuronal activity and eventually causes poor modulation of pain messages. With the emergence of Virtual Reality (VR) in acute pain management, and the contraindications of opioids in chronic pain, applying novel biotechnologies seems like the next frontier in multimodal pain management. In this study, the VR and NFB technologies were fused together (VR-NFB) and used as a novel treatment modality for a 55-year-old woman who suffered from chronic pain secondary to spondylolisthesis with cervical, thoracic, and lumbar disc herniations after a motor vehicle accident with comorbid depression, anxiety, sleep deprivation, and difficulty with activities of daily living, and inability to participate in physical therapy. Our case reports on the sustained analgesia achieved for 1 year after a trial of VR-NFB, and the usefulness of neuromodulation in centralized pain syndromes.

Keywords: virtual reality, neurofeedback, analgesia, centralized pain, neuromodulation

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INTRODUCTION

In neuropsychiatry, it is known that 20–40 NFB sessions are required for the neurofeedback's rehabilitating effect to be permanent. Because of neuroplasticity, the brain has the capacity to store traumatic experiences as well as learn new, healthy behaviors through new synaptic connections. This intervention was designed in the 1970s to activate the brain's inherent self-repairing mechanisms. Traditional neurofeedback has been shown to influence modulation of pain messages reaching the primary pain processing centers of the brain. The theory of central sensitization syndrome indicates that chronic physical pain becomes cognitive and emotional pain—or brain pain. Prolonged bombardment of the dorsal horn of the spinal cord possibly stimulates increased activation of neurons *via* the anterior spinothalamic pathway (ascending), leading to sensitization of the brain (1, 2). Chronic pain messages are modulated by the anterior cingulate gyrus, dorsolateral prefrontal cortex (DLPFC), and the insular cortex, as the three major postsynaptic pain-processing centers. Additionally, the thalamus and somatosensory cortex are involved in modulating pain messages (3), as well as the amygdala, under the direction of the medial prefrontal cortex (MPFC), which is involved in catastrophizing pain (4), and the affective component of the pain experience. Glutamate and substance P are two of the many neurotransmitters that are involved in lowering the threshold for the firing of the unmyelinated C fibers (5).

Virtual reality (VR) is a novel technology that has been shown in various studies to reduce acute pain as well as serving as an immersive distraction to pain. This process is probably carried out by the prefrontal cortex (PFC), which is responsible for the blocking of negative thoughts and feelings, distractions, and emotional regulation (6). In 1965, Melzack and Wall (7) came up with the gate theory that suggests that the amount of focus on pain, the emotional response to the pain, and the painful experience collectively influence how the brain will perceive the pain (7). Based on Wickens' (8) theory on multiple resources, the resources in different sensory areas of the brain all operate autonomously. It is obvious that the VR technology integrates the visual, auditory, and tactile sensory functions, while simultaneously distracting patients from their pain. Hoffman et al. (9) found that immersive VR during physical therapy helped lower pain scores significantly for burn victims. Another study by Sarig-Bahat et al. (10), found that a single session of VR alone where the patient sprayed flies in the game, improved range of motion in the cervical spine and reduced neck pain. Decades of research on NFB therapy has demonstrated the usefulness of this tool in mood disorders, sleep disorders, ADHD, neurological rehabilitation and, more recently, chronic pain. Research has shown that VR alone can reduce acute pain scores and minimize a patient's focus on pain. In this study, both technologies were combined as a novel clinical tool (VR-NFB) and was evaluated for its effectiveness as a treatment modality and its sustained analgesia for centralized pain.

CASE DESCRIPTION

A 55-year-old woman with a past medical history of cervical spine stenosis with radiculopathy, post-concussive syndrome, sciatica, status post motor vehicle accident (MVA), with a past psychiatric history of depression, anxiety, chronic pain syndrome, and PTSD related to the MVA, who presented with persistent right-sided shoulder and neck pain. She reported poor sleep quality and stated that she was not yet a candidate for surgery per the four different orthopedic and neurosurgical evaluations she underwent. She was visibly anxious, irritable, and tearful as she replayed the MVA in her mind. "Every time I come to a stop sign, my palms sweat, my heart races, I tense up, paranoid that someone will hit me from behind each time." She had recently visited the emergency room for acute exacerbation of her cervical pain with complaints of stiffness, right upper extremity radiculopathy, worsening neck pain, decreased range of motion (**Figure 1**), and inability to sleep and perform activities of daily living (ADLs) (**Figure 1**). She was prescribed the following oral medications: meloxicam 15 mg, gabapentin 100 mg three times daily, amitriptyline 10 mg nightly, cyclobenzaprine 10 mg as needed and memantine 5 mg per day. She reported that gabapentin had partially helped in the past but was no longer effective.

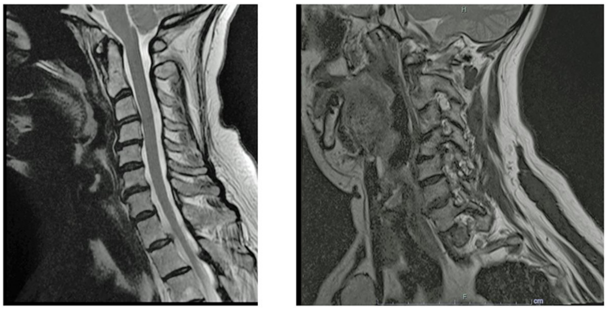

FIGURE 1 | MRI impression: Bilateral foraminal stenosis at C4 and C5, related to uncovertebral arthropathy, with exiting C5 nerve root impingement. At C5–C6, there is significant right foraminal stenosis with exiting C6 nerve root impingement. Photo courtesy of Joseph A. Marchione, MD, Neuroradiologist at Garnet Health Medical Center.

IMAGING

MRI of Cervical Spine

Treatment and Clinical Course

Materials and software used are the Oculus Rift-S VR headset (2019), the EEG NeuroAmp, and the Cygnet Software for the neurofeedback functions, all provided by BeeMedic. The patient was assisted with placing the headset over her head and over the leads for maximum comfort, and she was given prompts to stare at the game she wanted to play so it could load and begin. The patient underwent a clinical trial of 20 sessions of VR-NFB Therapy, completing two sessions weekly for a total of 10 weeks. The patient was screened with a thorough clinical history prior to starting VR-NFB. She had no history of thalamic strokes or traumatic brain injury, which were exclusion criteria. The patient was optimized at a frequency of 0.15 mHz at T3–T4, and T4–P4 at 0.175 mHz, for 20 total sessions. The Wong-Baker Pain Scale was used to identify the level of pain she experienced on a daily basis, as well as the level of anxiety, sleep, depression, PTSD symptoms, fatigue, and any interference in IADL/ADLs associated with the pain. Before each session began, she was asked about her level of distress using Subjective Unit of Distress before (BSUD) and then again at the end (ESUD) to observe for any acute change in the metrics.

Generally, the patient continued to struggle with fluctuations in pain intensity and reported an average pain score of 6 prior to starting VR-NFB sessions, with an average pain score of 4.5 status post VR-NFB session (15% improvement per session).

After 20 VR-NFB sessions the patient was evaluated for any change to her symptoms since starting the clinical trial. Her pain score (see **Figure 2**) improved from 9 to 5, indicating a 40% decrease in pain at the end of the trial. Her activities of daily living (ADLs) improved by 40% while her independent activities of daily living (IADLs) improved by 50%. Patient initially reported pain-related anxiety with a score of 8, which decreased to 4 after 20 VR-NFB sessions (40% improvement). She initially reported trouble falling asleep and staying asleep because of her chronic pain, reporting sleep deprivation as 10 out of 10, improving only to an 8 (20% improvement) after the clinical trial. Her

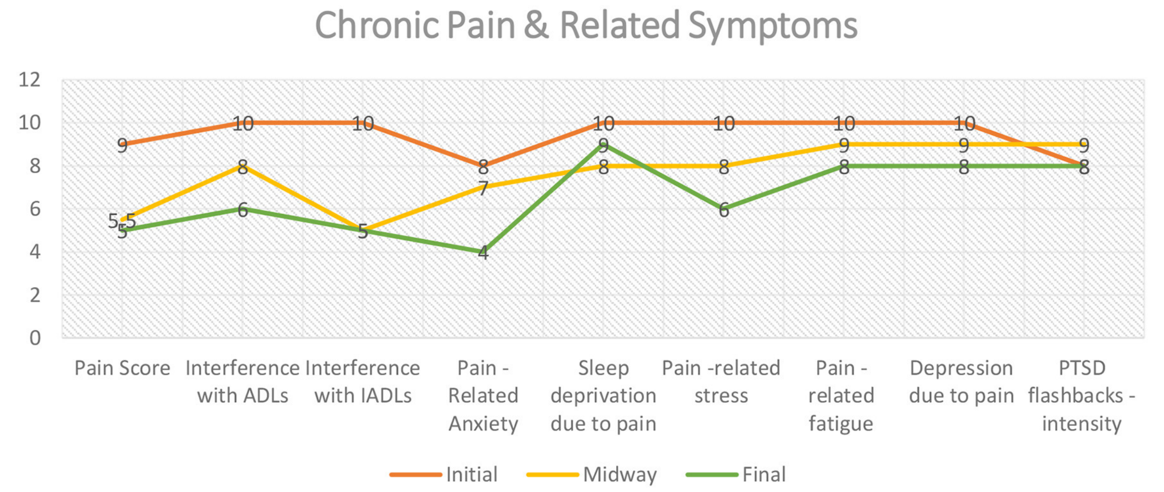

FIGURE 2 | Chronic pain intensity & pain-related symptoms.

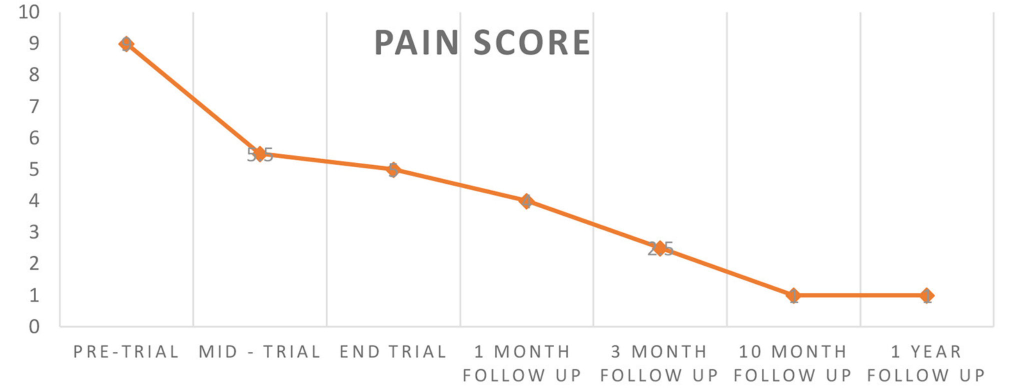

FIGURE 3 | Pain score—pre, mid, end trial and follow up—please refer to text.

scores for pain-related fatigue and pain-related depression were similar to that of sleep deprivation with a 20% improvement. She had no change in the intensity of her PTSD flashbacks post therapy vs. initial (**Figure 2**). As for her medications, she was able to completely discontinue gabapentin for neuropathic pain and cyclobenzaprine for cervicalgia and neck spasms; she began taking meloxicam less frequently because "it practically does nothing anymore." She continued her amitriptyline at the same dose and frequency.

POST-TREATMENT FOLLOW UP

At the end of the 20-session trial, she reported that her pain was at 5 out of 10 (40% improvement). The research team followed up with the patient at 1, 3, and 10 months. At 1 month, she reported that her pain score was at 4 out of 10, and declining. At the 3 months follow up, she reported that her pain continued to improve, reporting a pain score of 2.5 (mild) out of 10, and she reported a pain score of 1 at the 10-month and 1-year post trial follow up, indicating an overall improvement in pain of 80% from initial to 1-year follow up (**Figure 3**). This improvement in pain has allowed her to participate in physical therapy, while maintaining analgesia.

DISCUSSION OF OUTCOMES

This study explores VR-NFB as a non-opioid treatment for chronic pain. Virtual Reality Neurofeedback (VR-NFB) helped the patient experience an 80% improvement in pain from initial to 1 year follow up, with improvements in ADLs, anxiety, depressive symptoms, and sleep, while discontinuing Gabapentin for neuropathy, muscle relaxants, high dose Naproxen, and TCA medications known for cardiac side effects. In fact, literature and clinical data are reporting the role of pain, particularly chronic pain, as an important stressor on mental health and its relationship with everyday world stimuli. At her 1-year follow up, the patient reported that analgesia was sustained, her pain was more manageable, and she stated that the pain is hardly noticeable. She reported feeling happier, less anxious, and she was sleeping more than 6 hours nightly. She stated that her colleagues noticed she was brighter and less irritable, and less depressed to the extent of being able to discontinue amitriptyline with the help of her primary care physician.

LIMITATIONS AND STRENGTHS

The fact that this is a case report is an obvious limitation, and the study could possibly be improved by using other measurements for the affective components of pain like the Patient Health Questionnaire (PHQ-9) for evaluating the severity of depression and response to therapy, or the Beck Anxiety Inventory (BAI), used to measure severity of anxiety weekly. The strengths of this study is its focus on alleviating chronic pain from a neuropsychiatric perspective, and its employment of novel technologies to mitigate opioid dependence and reduce polypharmacy and improve resilience. Further, a strength of this study was that the VF-NFB therapy helped the patient achieve sustained analgesia for more than 1 year compared to the short-term pain relief in previous studies (9, 10) that used VR alone.

CONCLUSION

While traditional forms of neurofeedback have been shown to improve acute and central neuropathic pain in other studies, and VR alone has been shown to improve acute pain, VR-NFB is a novel approach that incorporates an additional analgesic effect of immersive distraction in the short term. This additional analgesia may be related to a beta endorphin-induced increase in dopamine in the mesolimbic pathway of the brain when a patient is engaged, experiencing pleasure, excited, seeking reward, or exploring newness. This acute increase in dopamine may enhance compliance in chronic pain patients, as they find pleasure in the VR-NFB therapy and its rewards, while actually anticipating therapy. Through its modulatory effect and change in neurochemistry, this novel treatment proved effective in sustained analgesia, and may provide permanent pain relief. We will follow up with the patient in 2 years to determine if the effects are permanent. Our case reports a 55-year-old woman who was able to experience long lasting pain relief and discontinue multiple medications that have cardiac side effects. This novel treatment could assist psychiatrists and practitioners in psychology in augmenting cognitive behavioral therapy for chronic pain (CBT-CP), while inadvertently eliminating polypharmacy. VR-NFB may serve as an adjunctive therapy in the toolkit of multimodal pain management. We have provided evidence that this therapy is non-invasive and effective in sustaining pain relief, while improving ADLs, anxiety, depression, and sleep, and eliminating polypharmacy, leading to overall improved resilience and self-regulation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Dr. Cleveland Lewis, MD, Dr. Pamela Murphy MD, and Dr. Eleonora Feketeova. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NO initiated the concept, design, data collection, analysis, and interpretation of the study. UV contributed to the final revision of the manuscript. CC-N contributed to the revision of the final manuscript. All authors contributed to the article and approved the submitted version.

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Awe/Gratitude as an Experiential Aspect of Spirituality and Its Association to Perceived Positive Changes During the COVID-19 Pandemic

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Background: While the COVID-19 pandemic has affected the lives of almost all people worldwide, many people observed also positive changes in their attitudes and behaviors. This can be seen in the context of posttraumatic growth. These perceived changes refer to five main categories: Nature/Silence/Contemplation, Spirituality, Relationships, Reflection on life, and Digital media usage. A previous study with persons recruited in June 2020 directly after the lockdown in Germany showed that the best predictors of these perceived changes related to the Corona pandemic were the ability to mindfully stop and pause in distinct situations, to be "spellbound at the moment" and to become "quiet and devout," indicating moments of wondering awe, with subsequent feelings of gratitude. Now, we intended to analyze (1) by whom and how strongly awe/gratitude was experienced during the COVID-19 pandemic, and (2) how these feelings relate to perceived changes and experienced burden, and (3) whether or not feelings of awe/gratitude contribute to participants' well-being or may buffer perceived burden in terms of a resilience factor.

Methods: Online survey with standardized questionnaires [i.e., WHO-Five Well-being Index (WHO5), Life satisfaction (BMLSS), Awe/Gratitude scale (GrAw-7), and Perceived Changes Questionnaire (PCQ)] among 2,573 participants (68% women; mean age 48.7 ± 14.2 years, 74% with a Christian affiliation) from Germany recruited between June and November 2020.

Results: Awe/Gratitude scored significantly higher particularly among women (Cohen's $d = 0.40$), older persons ($d = 0.88$), persons who rely on their faith as a "stronghold in difficult times" ($d = 0.99$), those with higher well-being ($d = 0.70$), and lower perceptions of loneliness ($d = 0.49$). With respect to perceived changes during the pandemic, more intense feelings of Awe/Gratitude were particularly related to Nature/Silence/Contemplation ($r = 0.41$), Spirituality ($r = 0.41$), and Relationships ($r = 0.33$). Regression analyses revealed that the best predictors of Awe/Gratitude ($R^2 = 0.40$) were the frequency of meditation, female gender, life satisfaction and well-being, faith as a stronghold, and perceived burden and also life reflection, while Nature/Silence/Contemplation and Relationships had a further, but weaker, impact on Awe/Gratitude as a dependent variable. Awe/Gratitude was moderately associated with well-being ($r = 0.32$) and would predict 9% of participants' well-being variance. The best predictors of participants' well-being were multidimensional life satisfaction and low perceived burden (related to the pandemic), and further Awe/Gratitude and Nature/Silence/Contemplation; these would explain 47% of variance in well-being scores. However, Awe/Gratitude cannot be regarded as a buffer of the negative aspects of the COVID-19 pandemic, as it is only marginally (though negatively) related to perceived burden ($r = -0.15$). Mediation analysis showed that Awe/Gratitude mediates 42% of the link between well-being as a predictor on Nature/Silence/Contemplation as an outcome and has a direct effect of $\beta = 0.15$ ($p < 0.001$) and an indirect effect of $\beta = 0.11$ ($p < 0.001$). Further, Awe/Gratitude mediates 38% ($p < 0.001$) of the link between Nature/Silence/Contemplation as a predictor on well-being as the outcome; the direct effect is $\beta = 0.18$ ($p < 0.001$), and the indirect effect is $\beta = 0.11$ ($p < 0.001$).

Conclusions: The general ability to experience Awe/Gratitude particularly during the COVID-19 pandemic may sensitize to perceive the world around (including nature and concrete persons) more intensely, probably in terms of, or similar to, posttraumatic growth. As this awareness toward specific moments and situations that deeply "touch" a person was higher in persons with more intense meditation or prayer practice, one may assume that these practices may facilitate these perceptions in terms of a training. However, the experience of Awe/Gratitude does not necessarily buffer against adverse events in life and cannot prevent perceived burden due to the corona pandemic, but it facilitates to, nevertheless, perceive positive aspects of life even within difficult times. As Awe/Gratitude is further mediating the effects of Nature/Silence/Contemplation on well-being, intervention programs could help to train these perceptions, as these self-transcendent feelings are also related to prosocial behaviors with respectful treatment of others and commitment to persons in needs, and well-being.

Keywords: awe, gratitude, spirituality, resilience, burden, perceived changes, COVID-19 pandemic

INTRODUCTION

The COVID-19 pandemic has changed the lives of almost all people worldwide in one way or the other. Many infected persons have died, others have recovered but have to cope with chronic health affections, and others recovered without relevant restrictions; a lot of people have lost their jobs, or are working in short-time, while others are in home-office or continue at their workplace. Many persons at risk avoid social contacts and feel isolated (1, 2), while others do not care too much about social restrictions (3), or even discuss why face-mask usage might be harmful (4). There are, in fact, heterogeneous ways to cope with the implications of the pandemic (5). A recent systematic review underlines that in the general population, there is a high prevalence of stress, anxiety, and depression because of the COVID-19 pandemic (6). Clinicians meet patients in depressive states and others with signs of "defeat stress" (7). Tumor patients, as an example of persons at risk, reported to be in fear of being infected, of having and complicated courses of disease and of staying helpless; they were irritated about conflicting information about the danger and about the course of the COVID-19 infection in the media (1, 2).

Nevertheless, related to the "extra time" at home during the lockdown, many people not only had fears and worries; they also perceived positive changes in their attitudes and behaviors. Tumor patients, for example, perceived nature and silence and also their relationships more intensely, some had a stronger interest in spiritual issues, while others perceived loneliness and ruminated worrying reflections (2). In a survey among a more general population from Germany, these perceived changes were operationalized and measured in terms of (1) *Nature/Silence/Contemplation*, (2) *Spirituality*, (3) *Relationships*, (4) *Reflection on life*, and (5) *Digital media use* (8). Strongest changes were observed for *Relationships* and *Nature/Silence/Contemplation*. All perceived changes were stronger among older persons, among those with higher well-being, and those who relied on their faith as a resource. Interestingly, best predictors of these perceived changes were the ability to mindfully stop and pause in distinct situations, to be "spellbound at the moment" and to become "quiet and devout," indicating moments of wondering awe, with subsequent feelings of gratefulness (8).

Perceptions of wondering awe, which can be considered as a variety of religious experience (9) can also be interpreted as an experiential aspect of "secular spirituality" as no specific religious belief is required and thus can be perceived also by non-religious persons (10, 11). Awe in terms of admiration (as a weaker experience) or even of overwhelming astonishment (as a stronger experience) is an emotional perception triggered by "outstanding" experiences, situations, nature, music, and persons (12–14). Keltner and Haidt (12) assumed that perceptions of awe might be experienced also in "times of tremendous social change;" in consequence, this perception is probably relevant particularly in times of the COVID-19 pandemic, too.

In line with the findings of Yaden et al. (15), qualitative analyses revealed that the range of awe triggers is wide, encompassing, e.g., Experience of nature, Perceiving the sacred in creation, Encounter with impressive people, Birth/own children, Accompanying the dying, Professional situations/Crises, Times of silence, Art and Music, Sacred buildings, and Special spiritual practices/ceremonies (Büssing et al., in preparation). Depending on the triggers, the resulting emotions can be overwhelming, while smaller moments of wonder (or admiration) are more common. The readiness to be touched and to mindfully perceive such moments seems to be higher in religious persons compared with non-religious/non-spiritual persons (10, 11). As Awe/Gratitude is related to the frequency of spiritual practices (i.e., meditation and praying), these practices can be considered as sensitizers for mindful encounters with nature, others, and with whatever a person may regard as sacred (10). Praying and meditation seem to facilitate such perceptions of connectedness with nature and others. Such a sense of connection and belonging was observed by Prade and Saraougly (16), too.

In Franciscan brothers and sisters, who have committed themselves to live a devoted life, which may facilitate such feelings, Awe/Gratitude was related to their intention to seek God in silence and prayer, with peaceful attitudes and respectful treatment of others and nature, and special care for persons in need (17). In terms of an "inner transformation," these perceptions may have consequences for a person's life, as they may change their behaviors and attitudes (12, 17). Self-transcendent emotions may also intensify a person's spirituality and their religious and spiritual feelings (18). Further, persons with a gratefulness disposition seem to be more able to perceive these feelings (10), and even persons with depressive diseases can experience them (19).

At any rate, Awe/Gratitude as a construct of spiritual awareness can be regarded as an additional dimension of a persons' quality of life. However, Awe/Gratitude is weakly associated with well-being and marginally only correlated to multidimensional life satisfaction (17). When one perceives awe in terms of the Sacred (God), then one may also feel more connected with others and may be more satisfied with life (20). In addition, gratitude as a life orientation is associated with well-being and positive social relationships (21), and with lower risk of major depression, generalized anxiety disorder, phobia, and drug abuse (22), as it may help to reframe the negative emotions (23). For religious persons, gratitude is also related with perceived closeness to God and to a secure attachment to God (24). Furthermore, spiritual transcendence and connectedness with transcendent sources of meaning outside is higher in grateful persons (25).

On the other hand, therefore, well-being is not necessarily a prerequisite to perceive Awe/Gratitude. Feelings of Awe/Gratitude may arise because of a more open and mindful awareness for those things in life that are of value and thus can emotionally touch a person—in spite of difficulties in life (i.e., coping with the outcomes of the COVID-19 pandemic). Such an awareness shift has been frequently observed in persons who undergo difficult life situations or phases of illness (26). In this perspective, one can even relate the outcomes of these experiences to the concept of posttraumatic growth (27, 28) or of spiritual transformation (29, 30), where people change their attitudes and make new resolutions, become (at least for some time) more conscious, more attentive, more mindful, more spiritually minded, etc.

As perceptions of awe and gratitude were among the best predictors of persons' perceived changes due to the Corona pandemic (2), we intended to analyze whether Awe/Gratitude could be regarded as a resilience factor to cope with the impacts of the pandemic on their lives. Theoretical considerations drawn from experimental studies would indicate that awe may buffer negative feelings (31, 32). Also in an experimental group of people waiting for the results of an intelligence test or peer feedback, positive emotions and less anxiety were observed when they experienced "awe conditions" compared with neutral conditions, and these findings were independent from a person's predisposition to experience awe (33). As positive emotions usually help to adapt in difficult situations, it was suggested that also gratitude could be a resilience factor [(34); cf. (35)]. We therefore intended to analyze (1) how strongly and by whom Awe/Gratitude was perceived during the corona pandemic, and (2) how these feelings relate to perceived changes and experienced burden during the pandemic, and (3) whether or not feelings of awe/gratitude contribute to participants' well-being or may buffer perceived burden.

METHODS

Recruitment of Participants

Participants were recruited within 6 months (from June 9 to November 30, 2020). The snowball sampling started in

TABLE 1 | Sociodemographic data of participants ($N = 2,573$).

	n	% of responders	Mean ± SD	Range
Gender				
Women	1,443	67.9		
Wen	821	32		
Age (years)	1,261		48.7 ± 14.2	15–92
Living conditions				
Family household	1,664	64.7		
Shared house	229	8.9		
Single	515	20		
Monastery/community	180	7		
Profession*				
Administration	368	14.3		
Economy	243	9.4		
Education	285	11.1		
Medicine/health	527	20.5		
Church	434	16.9		
Other	913	35.6		
Religious affiliation				
Catholics	1,331	51.7		
Protestant	569	22.6		
Other	105	4.1		
None	570	22.2		
Faith as stronghold in difficult times				
Disagreement	705	28,1		
Undecided	728	29.1		
Agreement	1,072	42.8		
Meditation			1.2 ± 1.2	0–3
Never	1,054	44.3		
At least once per month	345	14.5		
At least once per week	449	18.9		
At least once per day	530	22.3		
Praying			1.6 ± 1.3	0–3
Never	821	34.6		
At least once per month	267	11.3		
At least once per week	378	15.9		
At least once per day	905	38.2		
Physical activity/sporting			1.8 ± 0.9	0–3
Never	354	14.9		
At least once per month	348	14.6		
At least once per week	1,217	51.1		
At least once per day	461	19.4		
Walking outside in nature			2.1 ± 0.8	0–3
Never	83	3.5		
At least once per month	388	16.2		
At least once per week	1,236	51.6		
At least once per day	690	18.8		
Wellbeing and burden				
Life satisfaction (BMLSS-10)	2,573		67.2 ± 16.1	0–100
Satisfaction with Support (BMLSS Support)	2,571		60.6 ± 18.2	0–100
Wellbeing (WHO-5 100)	2,572		58.7 ± 22.2	0–100
Wellbeing (WHO-5 sum)	2,573		14.7 ± 5.5	0–25
Low wellbeing (WHO-5 sum scores <13)	835	32.5		
Moderate wellbeing (WHO-5 sum scores 13–18)	973	37.8		
High wellbeing (WHO-5 sum scores >18)	765	29.7		
Perceived burden ("Stressors") (5NRS)	2,572		31.0 ± 20.9	0–100
Loneliness/social isolation (NRS)	2,572		25.0 ± 28.5	0–100
No loneliness (NRS scores = 0)	900	35		
Low to moderate loneliness (NRS cores 10–50)	1,245	48.4		
High loneliness (NRS scores 50–100)	427	16.6		
Perceived changes (PCQ)				
Nature/Silence/Contemplation	2,549		56.6 ± 21.0	0–100
Spirituality	2,549		41.8 ± 26.0	0–100
Relationships	2,551		63.3 ± 18.9	0–100
Reflection on life	2,549		52.3 ± 25.0	0–100
Digital media usage	2,548		54.5 ± 23.7	0–100

Some ascribed themselves to multiple professions, and thus, the response rate is >100%.

different networks in Germany, i.e., university students and staff, research collaborators, religious orders and church communities, Rotary Club members, Facebook sites, diocesan websites, etc. All contacted persons and networks were invited to share the information and link where possible. Within this time frame, we were able to include persons from the first wave of the corona pandemic, from the "relaxation" time in summer, and in the meantime from the second wave of fall and winter 2020.

Participants were assured confidentially and were informed about the purpose of the study and data protection information at the starting page of the online survey. By filling in the anonymous questionnaire, interested persons consented to participate. Neither concrete identification of personal details nor IP addresses were recorded to realize and guarantee full anonymity. Therefore, we were unable to control for multiple entries.

TABLE 2 | Items and response rate of the Awe/Gratitude scale.

		Never (%)	Seldom (%)	Often (%)	Very often (%)	Mean score (0–3)
ED1	I have a feeling of great gratitude.	3	21	52	25	1.99 ± 0.75
ED2	I have a feeling of wondering awe.	10	44	36	11	1.48 ± 0.82
ED3	I still have learned to experience and value beauty.	1	9	57	33	2.23 ± 0.63
ED4	I stop and am captivated by the beauty of nature.	1	13	46	40	2.24 ± 0.71
ED5	I pause and stay spellbound at the moment.	3	38	43	17	1.74 ± 0.76
ED6	In certain places I become very quiet and devout.	3	31	46	21	1.84 ± 0.78
ED7	I stop and then think of so many things for which I am really grateful.	3	28	48	21	1.88 ± 0.77

Awe and Gratitude

To address times of pausing for "wonder" (Awe) in specific situations as a perceptive aspect of spirituality, we used the seven-item Awe/Gratitude scale (GrAw-7) (10). This single-factor scale has good psychometric properties (Cronbach's alpha = 0.82) and uses items such as "In certain places, I become very quiet and devout," "I stop and am captivated by the beauty of nature," "I pause and stay spellbound at the moment," "I stop and then think of so many things for which I'm really grateful." The scale thus addresses a person's emotional reaction toward an immediate and "captive" experience. All items were scored on a four-point scale (0—*never*; 1—*seldom*; 2—*often*; 3—*regularly*), referred to as a 100-point scale. In this sample, Cronbach's alpha is 0.87, and the single-factor structure was confirmed (explaining 57% of variance).

Perception of Changes

Perceived changes due to the Corona pandemic were measured with the 24-item Perceived Changes Questionnaire (PCQ) (8). This newly developed instrument differentiates five dimensions (factors) with good internal consistence: (1) *Nature/Silence/Contemplation* (Cronbach's alpha = 0.87), (2) *Spirituality* (Cronbach's alpha = 0.83), (3) *Relationships* (Cronbach's alpha = 0.80), (4) (worrying) *Reflection on life* (Cronbach's alpha = 0.74), (5) *Digital media usage* (Cronbach's alpha = 0.74). The respective items refer to perceptions that were reported by various persons at the start of the COVID-19-related lockdown. The respective items were introduced by the phrase "Due to the current situation…," (referring to the Corona pandemic) and scored on a five-point agreement scale (0—*does not apply at all*; 1—*does not truly apply*; 2—*neither yes nor no*; 3—*applies quite a bit*; 4—*applies very much*). Specific items are "I perceive the relationship with my partner/family more intensely," "I pay more attention to what's really important in life," "I perceive nature more intensely," "I enjoy quiet times of reflection," "I am connected to friends via digital media," "I deal more with spiritual/religious questions," "I pray/meditate more than before," "I'm more concerned about the lifetime that I have," etc.

Well-Being Index

Participants' well-being (within the last 2 weeks) was measured with the WHO-Five Well-being Index (WHO-5) (36). It uses items such as "I have felt cheerful and in good spirits" or "My daily life has been filled with things that interest me." The frequency of these experiences is scored from *at no time* (0) to *all of the times* (5). Here, we report the sum scores ranging from 0 to 25 and also the 100% level scores ranging from 0 to 100. Scores <13 (or <50) would indicate reduced well-being or even depressive states. In this sample, Cronbach's alpha = 0.89.

Life Satisfaction

Life satisfaction was measured with the Brief Multidimensional Life Satisfaction Scale (BMLSS) (37). It covers five main topics: intrinsic (oneself and life in general), social (friendships and family life), external (work situation and where one live), prospective dimensions (financial situation and future prospects), and health (health situation and abilities to deal with daily life concerns). All items were scored on a seven-point scale from dissatisfaction to satisfaction (0—*very dissatisfied*; 1—*dissatisfied*; 2—*mostly dissatisfied*; 3—*mixed (about equally satisfied and dissatisfied)*; 4—*mostly satisfied*; 5—*satisfied*; 6—*very satisfied*). The BMLSS score was referred to as a 100% level (transformed scale score). The internal consistency of the instrument was found to be good in the validation study (Cronbach's alpha = 0.87). In this sample, Cronbach's alpha = 0.82.

Perception of Burden

Perceived restrictions of daily life, of being under pressure/stressed, anxiety/insecurity, loneliness/social isolation, and financial-economic situation due to corona pandemic were measured with five numeric rating scales (5NRS), ranging from 0 (*not at all*) to 100 (*very strong*) as described (8). These five variables can be combined to a factor termed "Perceived burden" ("Stressors") with good internal consistency (Cronbach's alpha = 0.80).

Indicators of Spirituality

To measure reliance on faith, item A37 from the Reliance on God's Help scale (38) was used as a differentiating variable to assess intrinsic religiosity in terms of an attitude. It states "faith as a stronghold in difficult times" and can be scored on a three-point scale (0—*disagreement*; 2—*indifference*; 3—*agreement*). The frequency of spiritual/religious practices such as meditation or praying was assessed with a four-grade scale ranging from *never*, to *at least once per month*, *at least once per week*, and *at least once per day* as described (2, 8).

Physical Activities

We addressed physical activity/sporting and walking outside in nature with a four-grade scale (*never*, *at least once per month*, *at least once per week*, and *at least once per day*) as described (2, 8). When awe is indeed triggered by experience in nature, etc., then a positive association with walking outside in nature can be expected, but intuitively, not that intensely, with physical activity/sporting.

Statistical Analyses

Descriptive statistics for demographic variables and for factors are presented as frequencies for categorical variables and mean (±standard deviation, SD) for numerical variables. Analyses of variance (ANOVA) as well as first-order correlation (Spearman rho) and linear regression analyses with stepwise variable selection method based on probabilities (p-values) were computed with SPSS 23.0. To investigate possible interactions as mediation and moderation of independent variables on dependent factors, the Mediation and Moderation Analyses were performed with software R (4.0.3) packages "mediation" (39) and "olsrr" (40). Given the exploratory character of this study, we set a stricter significance level at $p < 0.01$ (41). With respect to classifying the strength of the observed correlations, we adjusted the recommended thresholds (42) to $r > 0.5$ as a strong correlation, an r between 0.3 and 0.5 as a moderate correlation, an r between 0.2 and 0.3 as a weak correlation, and $r < 0.2$ as negligible or no correlation. Cohen's d effect sizes were used to report differences between groups (43).

RESULTS

Description of the Sample

Within the sample ($N = 2.573$), women (68%) and persons with a Christian affiliation (74%) were predominating (**Table 1**). Participants' mean age was 48.7 ± 14.2 years. Their area of profession was heterogeneous, ranging from Administration, Economy, Education, Medicine/Health, Church, and other (incl. students and retired persons). Despite a predominance of Christian and other religious affiliations (78%), only 43% stated to have faith as a stronghold in difficult times, 29% were undecided, and 28% disagreed. In line with this proportion, 38% were praying at a daily level (indicating a religious person) and 22% meditating at a daily level, while 44% were never meditating and 35% never praying. Physical activities/sporting and walking outside in the nature were practiced by 71 and 70%, respectively, at least once per week (**Table 1**).

Within the sample, life satisfaction and well-being were in a moderate range. Thirty-two percent have WHO-5 scores <13, indicating low well-being. Furthermore, 17% have strong feelings of loneliness/social isolation. However, participants' general perceived burden (5NRS) scored in the lower third, indicating that the majority of the participants were (only) "somewhat" affected (**Table 1**).

Participants perceived changes in their attitudes and behaviors due to the Corona pandemic, particularly with respect to *Nature/Silence/Contemplation* and *Relationships*, while changes in *Digital media usage* and *Reflection of life* were less strong; in contrast, changes in *Spirituality* were rather not perceived (**Table 1**).

TABLE 3 | Awe/Gratitude in different subgroups.

	Awe/Gratitude
All	63.74 ± 18.79
Gender	
Female	66.13 ± 18.32
Male	58.72 ± 18.79
F value	89.85
p value	<0.0001
Cohen's d (f/m)	0.40
Age cohorts	
<30 years	57.10 ± 17.92
30–40 years	57.20 ± 19.27
41–50 years	62.25 ± 19.06
51–60 years	67.04 ± 17.84
61–70 years	69.03 ± 16.96
>70 years	72.52 ± 16.62
F value	37.90
p value	<0.0001
Cohens' d (<30/>70)	0.88
Religious	
Living in Monastery	73.02 ± 15.32
All other	63.04 ± 18.84
F value	48.11
p value	<0.0001
Cohens' d (monastery/not)	0.60
Faith as stronghold	
Does not apply	53.67 ± 18.11
Partly	62.00 ± 16.25
Applies	71.36 ± 17.58
F value	225.56
p value	<0.0001
Cohens' d (yes/no)	0.99
Well-being (WHO-5)	
Scores <13	57.03 ± 18.50
Scores 13–18	63.85 ± 16.94
Scores >18	70.92 ± 18.68
F value	119.05
p value	<0.0001
Cohens' d (high/low)	0.70
Loneliness (NRS)	
Scores 50–100	57.67 ± 19.95
Scores 10–50	63.23 ± 17.17
Scores = 0	67.32 ± 19.56
F value	40.31
p value	<0.0001
Cohens' d (high/low)	0.49

Perception of Awe and Gratitude

Within the sample, stopping and being "captivated by the beauty of nature" and "experience and value of beauty" were experienced

TABLE 4 | Correlations between Awe/Gratitude and other variables.

	Awe/Gratitude
Perceived Changes (PCQ)	
Nature/Silence/Contemplation	0.408**
Spirituality	0.407**
Relationships	0.333**
Reflection on life	0.257**
Digital media usage	0.146**
Restrictions	–0.174**
Well-being and burden	
Life satisfaction (BMLSS-10)	0.289**
Well-being (WHO-5)	0.316**
Perceived burden (5NRS)	–0.153**
Frequency of activities	
Physical activities/sporting	0.143**
Walking outside in nature	0.237**
Meditation	0.442**
Praying	0.365**

***p < 0.001 (Spearman rho); moderate associations are highlighted.*

most often (often to very often by 90 and 86%, respectively), followed by feelings of "great gratitude" (often to very often by 77%), while feelings of "wondering awe" were experienced less often (often to very often by 47%) (**Table 2**).

As shown in **Table 3**, Awe/Gratitude scored significantly higher particularly among women (Cohen's $d = 0.40$), older persons ($d = 0.88$), persons who rely on their faith as a "stronghold in difficult times" ($d = 0.99$), religious brothers and sisters ($d = 0.60$), those with higher well-being ($d = 0.70$), and lower perceptions of loneliness ($d = 0.49$). Further, Awe/Gratitude was moderately related to a person's meditation and praying frequency, and weakly to life satisfaction (particularly satisfaction with life in general, $r = 0.30$) and to walking outside in nature, and marginally only to physical activities/sporting (**Table 4**).

Relation of Awe/Gratitude to Perceived Changes Due to the Corona Pandemic

With respect to perceived changes in attitudes and behaviors because of the Corona pandemic, Awe/Gratitude was moderately related to *Nature/Silence/Contemplation*, *Spirituality* and *Relationships*, weakly also to *Reflection of life*, and marginally only *to Digital media usage* or perceived *Restrictions* (**Table 4**). Also, Perceived burden ("Stressors") related to the Corona pandemic was marginally (and inversely) related to Awe/Gratitude scores.

Predictors of Awe/Gratitude

As there are several variables significantly related to perceptions of Awe/Gratitude, both inherent and in response to the pandemic, regression analyses were performed to analyze which independent variables would predict Awe/Gratitude (as a dependent variable). These regression analyses were performed in different steps, which refer to previous findings (8): (1) including gender and age as independent variables, (2) adding spirituality-related variables (faith as a strong hold, meditation, and praying), (3) adding well-being and life satisfaction (which is related also to the feelings during the pandemic), and (4) adding perceived changes and burden because of the pandemic.

As shown in **Table 5**, higher age and female gender predicted 11% of Awe/Gratitude score variance (with age being the best predictor). Adding the three spirituality-related variables, the explained variance increased to 28% (now meditation frequency became the best predictor). Adding well-being and life satisfaction to the model in the third step, the included variables would explain 35% of variance (now age loses its relevance as a predictor). Adding the topics of perceived changes and perceived burden due to the corona pandemic raises the predictive power to 40%. Finally, the best predictors of Awe/Gratitude were frequency of meditation practice, female gender, life satisfaction and well-being, faith as a stronghold, perceived burden, and life reflection because of the pandemic. Perceived *Restrictions* and changes in spiritual practices and perceptions (*Spirituality*), and changed *Digital media usage* had no independent predictive relevance in this final model.

Predictors of Well-Being

Which of the analyzed variables would predict best a persons' well-being (as dependent variable) during the Corona pandemic? Awe/Gratitude (as an influencing variable) alone would predict 9% of participants' variance in their well-being, as regression analyses indicated. Stepwise regression analyses including the abovementioned independent variables revealed that it is foremost life satisfaction and low perceived burden (related to the pandemic), which would together explain 44% of well-being variance. Next, relevant variables were Awe/Gratitude and *Nature/Silence/Contemplation* (PCQ), which would add 3% of the explained variance. The next six significant predictors (low *Reflection of life*, higher age, walking outside in nature, low *Relationships*, female gender, physical activities/sporting) were of even less relevance as all of them together would add only 2% of the explained variance (**Table 6**). Not significant in this prediction model were frequency of Meditation and Praying, *Spirituality* (PCQ), and *Digital media usage* (PCQ).

Meditation and Moderator Analyses

It is supposed that Awe/Gratitude could play a role in the analysis either as mediator or moderator. For this purpose, both causal relationships will be investigated. Mediation analysis describes a causal sequence of effects from the predictor variable on the outcome. Moderator analysis evaluates if a given variable affects the direction and/or strength of the causal relationship (in terms of an "enhancer" or "buffer"). Mediation analysis revealed that Awe/Gratitude mediates 42% ($p < 0.001$) of the link between well-being as a predictor on *Nature/Silence/Contemplation* as an outcome and has a direct effect of $\beta = 0.15$ ($p < 0.001$) and an indirect effect of $\beta = 0.11$ ($p < 0.001$) (**Figure 1A**). Furthermore, Awe/Gratitude mediates 38% ($p < 0.001$) of the link between *Nature/Silence/Contemplation* as a predictor on well-being as the outcome; the direct effect is $\beta = 0.18$ ($p <$

TABLE 5 | Predictors of well-being as dependent variable (regression analyses).

	Beta	**T**	***p***	**Beta**	**T**	***p***	**Beta**	**T**	***p***	**Beta**	**T**	***p***
Dependent variable: GrAw-7 scores	**Model 1: $F = 135.6$. $R^2 = 0.11$**			**Model 2: $F = 157.7$. $R^2 = 0.28$**			**Model 3: $F = 154.6$. $R^2 = 0.35$**			**Model 4: $F = 95.5$ $R^2 = 0.40$**		
Constant		32.891	<0.0001		33.405	<0.0001		19.082	<0.0001		8.355	<0.0001
Male gender	−0.199	−10.081	<0.0001	−0.177	−9.300	<0.0001	−0.190	−10.482	<0.0001	−0.162	−9.157	<0.0001
Age cohorts	0.266	13.450	<0.0001	0.100	4.931	<0.0001	0.070	3.560	<0.0001	0.054	2.842	0.005
Faith as hold				0.180	6.669	<0.0001	0.144	5.584	<0.0001	0.105	3.972	<0.0001
Meditation				0.286	13.393	<0.0001	0.285	13.963	<0.0001	0.232	11.180	<0.0001
Praying				0.080	2.911	0.004	0.088	3.333	0.001	0.075	2.763	0.006
Well-being (WHO-5)							0.134	5.945	<0.0001	0.161	6.721	<0.0001
Life satisfaction (BMLSS-10)							0.164	7.382	<0.0001	0.184	8.019	<0.0001
Nature/Silence/Contemplation (PCQ)										0.084	3.190	0.001
Spirituality (PCQ)										0.025	0.805	0.421
Relationships (PCQ)										0.082	3.668	<0.0001
Reflection on life (PCQ)										0.101	4.232	<0.0001
Digital media usage (PCQ)										−0.020	−1.048	0.295
Perceived restrictions (PCQ)										−0.035	−1.582	0.114
Perceived burden (5NRS)										0.103	4.210	<0.0001

TABLE 6 | Predictors of well-being (stepwise regression).

Dependent Variable: Well-being (WHO-5) Model 10: $F = 196.3$, $p < 0.0001$; $R^2 = 0.49$	**Beta**	**T**	***p***
(constant)		5.984	<0.0001
Life satisfaction (BMLSS-10)	0.339	17.154	<0.0001
Perceived burden (5NRS)	−0.320	−16.578	<0.0001
Awe/Gratitude (GrAw-7)	0.123	6.535	<0.0001
Perceived Changes: Nature/Silence/Contemplation (PCQ)	0.168	7.251	<0.0001
Perceived Changes: Reflection of life (PCQ)	−0.115	−5.651	<0.0001
Age cohort	0.062	3.715	<0.0001
Walking outside in nature	0.049	2.907	0.004
Perceived Changes: Relationships (PCQ)	−0.059	−2.912	0.004
Female gender	0.046	2.801	0.005
Physical activities/sporting	0.039	2.407	0.016

Not significant in the model: Praying, Meditation, Satisfaction with support, Perceived Changes: Spirituality; Perceived Changes: Digital media usage.

0.001), and the indirect effect is $\beta = 0.11$ ($p < 0.001$) (**Figure 1B**). For *Relationships* as an outcome, Awe/Gratitude mediates 62% ($p < 0.001$) of the effect of well-being as predictor, with small direct and indirect effects of $\beta = 0.05$ ($p < 0.01$) and β = 0.08 ($p < 0.001$), respectively (**Figure 1C**). Finally, Awe/Gratitude mediates 95% ($p < 0.001$) of the effect of well-being on *Reflection of life*; interestingly, the direct effect $\beta = -0.26$ ($p < 0.001$) has a negative influence decreasing the intensity of *Reflections*, while the indirect effect $\beta = 0.12$ ($p < 0.001$) remains positive (**Figure 1D**). All other perceived changes were not significantly mediated by Awe/Gratitude. However, Awe/Gratitude was a significant mediator, but not a significant moderator of the link between perceived changes and well-being (data not shown).

Next, we analyzed whether well-being could moderate interaction effects between perceived changes (namely, *Nature/Silence/Contemplation*, *Spirituality*, and *Relationships*, and also Meditation or Praying) on Awe/Gratitude. Interestingly, Awe/Gratitude can be estimated through the variables *Nature/Silence/Contemplation* ($\beta = 0.11$), *Spirituality* ($\beta = 0.09$), *Relationships* ($\beta = 0.26$), well-being ($\beta = 0.26$), and meditation frequency ($\beta = 0.10$), but not significantly through frequency of praying ($\beta = 0.01$). The β values represent the standardized estimates of the regression model and are in the interval (0,1). In this model, well-being was moderating weakly the relationship between Awe/Gratitude and meditation ($\beta = 0.15$), praying ($\beta = 0.13$) and inversely also *Relationship* ($\beta = -0.21$), but not *Spirituality* or *Nature/Silence/Contemplation* (**Figure 2**). The respective model has a moderate adequacy explaining 36% of the variance in the data. Furthermore, no significant moderation model was observed for well-being as response variable (data not shown).

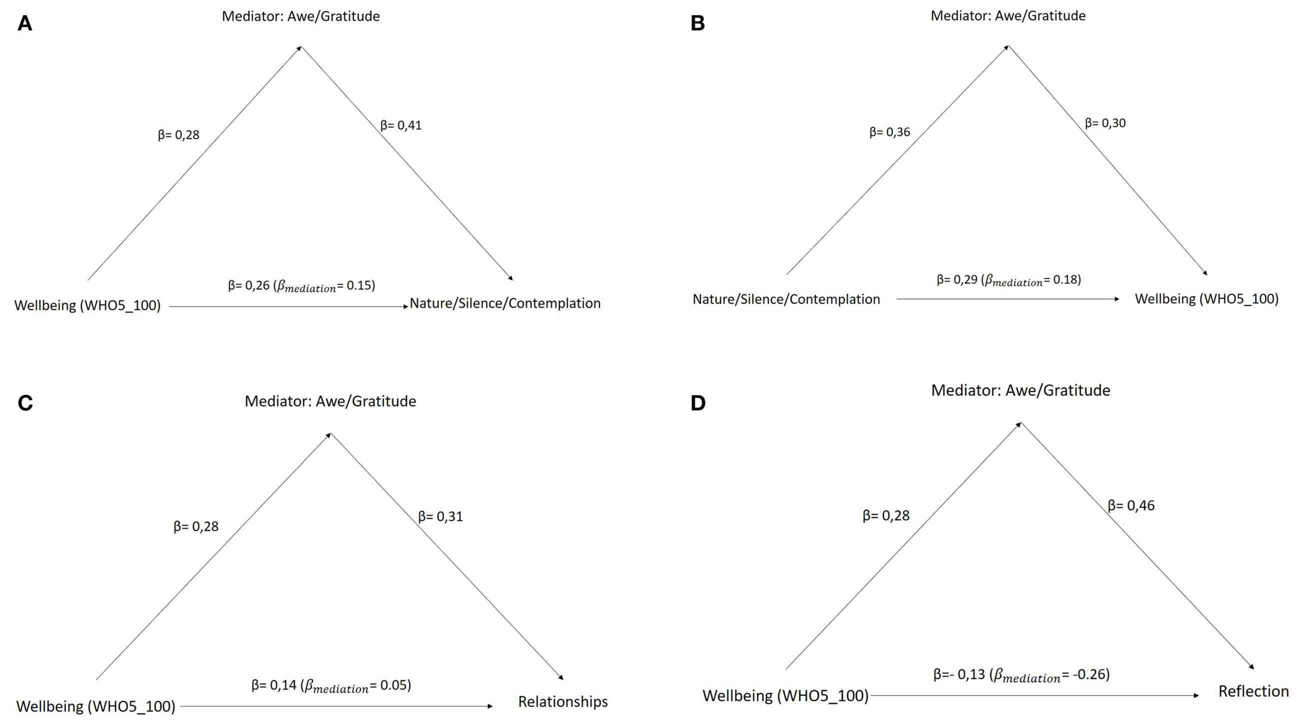

FIGURE 1 | Different mediation models with Awe/Gratitude as mediator. Well-being as predictor and Nature/Silence/Contemplation as outcome mediated by Awe/Gratitude **(A)**. The proportion of causal effect explained by the mediator is 42%, direct effect is 0.15, and total effect is 0.26. Nature/Silence/Contemplation as predictor and well-being as outcome mediated by Awe/Gratitude **(B)**. The proportion of causal effect explained by the mediator is 38%, direct effect is 0.18, and total effect is 0.29. Well-being as predictor and Relationships as outcome mediated by Awe/Gratitude **(C)**. The proportion of causal effect explained by the mediator is 62%, direct effect is 0.05, and total effect is 0.14. Well-being as predictor and Reflection as outcome mediated by Awe/Gratitude **(D)**. The proportion of causal effect explained by the mediator is 95%, direct effect is –0.26, and total effect is –0.13.

Course of Well-Being, Perceived Burden, and Awe/Gratitude Within the 6-Month Observation Period

Time of course may have significant influence on several variables. The main recruiting phase was within June and July 2020 ($n = 2{,}046$); nevertheless, we further recruited participants within the summer months August and September ($n = 288$) and during the autumn months October and November ($n = 242$), which went along with the start of the second wave of the COVID-19 pandemic in Germany. Referring to different cohorts, within these 6 months, participants' well-being decreased significantly [$F_{(2,2,575)} = 70.4$, $p < 0.0001$], while Perceived burden increased [$F_{(2,2,574)} = 100.8$, $p < 0.0001$] (**Figure 3**). Within this time span, feelings of Awe/Gratitude were significantly declining [$F_{(2,2,572)} = 54.6$, $p < 0.0001$]. This decline is more related to the decrease in well-being rather than to the increase in Perceived burden, as well-being and Awe/Gratitude are moderately correlated ($r = 0.32$, $p < 0.001$; Spearman rho), while the association between Perceived Burden and Awe/Gratitude is marginal only ($r = –0.15$, $p < 0.001$; Spearman rho). It has to be noted, however, that the participants of October to November are, on average, 5 years younger (mean age) than the participants of the months June to July [$F_{(2,2,546)} = 28.6$, $p < 0.0001$], while the gender proportion was similar ($p = 0.68$, Chi^2).

DISCUSSION

Answers to Our Research Questions

Referring to our research questions, first, we can state that particularly women, older persons, and religious/spiritual persons perceived Awe/Gratitude more often (and intensely); this is also true for those with higher well-being and lower perceptions of loneliness. It seems that both, low scores of well-being and feelings of loneliness may distract a person's awareness for the Sacred and the "beauty" in life. In persons with depressive states, their perception of beauty (in nature) was found to be lower compared with those of the other patients, while their general ability to stand in wondering awe and to be grateful was not significantly different (19). In this study, well-being was particularly related to feelings of gratefulness (item ED1: $r = 0.33$) and to the experience and value of beauty (ED3: $r = 0.30$), to stopping in awe and then thinking "of so many things for which I am really grateful" (ED7: $r = 0.28$). Thus, low emotional well-being is associated with low feelings (or felt reasons) of gratefulness in life, in general—and probably also during the pandemic, in particular. In this study, reduced well-being was strongly associated with dissatisfaction with oneself ($r = 0.56$), dissatisfaction with life, in general ($r = 0.54$), and dissatisfaction with own abilities to cope with daily life situations ($r = 0.50$). These more "personal" variables could be related to the underlying personality structure.

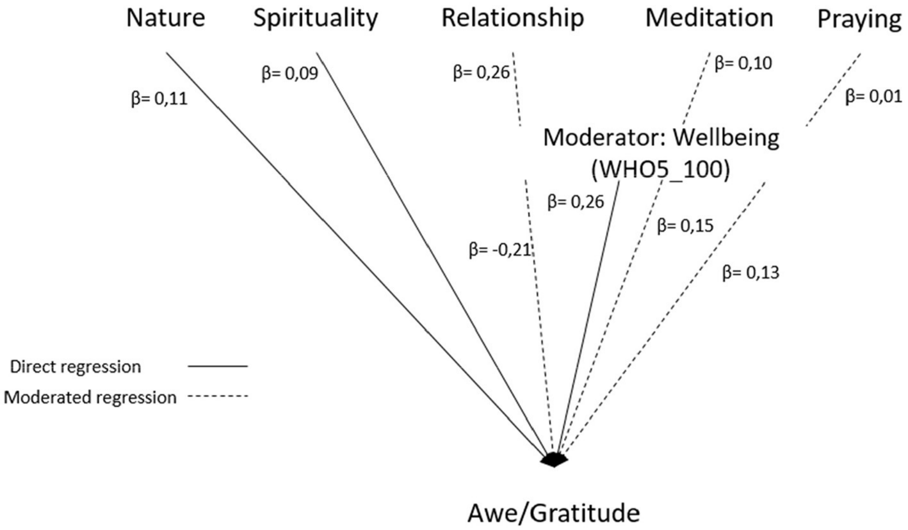

FIGURE 2 | Moderator model for Awe/Gratitude (GrAw), $R^2 = 0.36$, with well-being (WHO-5) negatively moderating the regression effect of Relationship, but positively moderating the effect of Meditation and Praying on Awe/Gratitude.

With respect to perceived changes during the pandemic as second focus, more intense feelings of Awe/Gratitude were particularly related to *Nature/Silence/Contemplation*, *Spirituality* and *Relationships*. This means that the general ability to experience Awe/Gratitude particularly during the Corona pandemic may sensitize to perceive the world around (including nature and concrete persons) more intensely. Furthermore, well-being modified the relation between *Relationships* and Awe/Gratitude decreasing the intensity of those feelings. This interaction indicates that *Relationships* might be a protective factor, but if well-being fluctuates in a lower range of scores, the potency of Awe/Gratitude degenerates. Apart from moderation effects, we found evidence that Awe/Gratitude is mediating the link between *Nature/Silence/Contemplation* and well-being and also in the reverse order between well-being and *Nature/Silence/Contemplation*. This means that the effect of well-being on the perception of changes related to nature, silence, and contemplation can be enhanced by Awe/Gratitude, on the one hand, and that the perceived changes related to nature, silence, and contemplation may positively influence a person's well-being, mediated by the ability to perceived Awe/Gratitude. Moreover, Awe/Gratitude weakly mediates the relationship between well-being and *Relationships* and negatively between well-being and *Reflection* of life. Well-being itself is a buffer for *Reflection of life* (which implies worrying thoughts about meaning and purpose in life and the lifetime one has, and more intensive perceptions of loneliness) and the mediator and may thus reduce the intensity of this effect, acting as an enhancer.

The underlying dynamics for the realization of this ability to perceive beauty in nature, to stand in wondering awe and finally to be grateful might be comparable or even the same as in posttraumatic growth (27, 28) or spiritual transformation (29, 30), processes in which people change their attitudes and make new resolutions because of specific experiences. Yaden et al. (15) likewise observed that the experience of awe may result in feelings of connectedness with others and nature. The realization of such dynamics seems to depend on various factors. The best predictors of Awe/Gratitude were the frequency of meditation (which may indicate that the awareness can be trained), female gender (women are usually more aware of their emotions and more sensitive toward spiritual issues) (44), life satisfaction, and well-being (which may indicate that positive emotional states may facilitate awareness), faith as a stronghold (which may imply that whatever may come, one has unconditional trust in God or another source of hope), and inversely and marginally only perceived burden and also life reflection (which has a negative worrying connotation in this context), too. *Nature/Silence Contemplation* and *Relationships* had a further, but weaker, impact on Awe/Gratitude as a dependent variable.

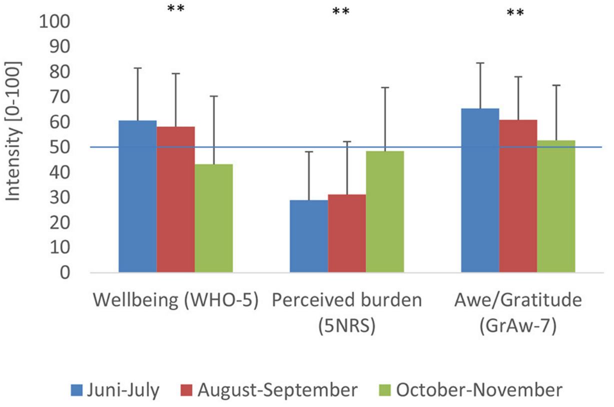

FIGURE 3 | Course of well-being, perceived burden, and awe/gratitude within the 6-month observation period (**$p < 0.0001$; Spearman rho).

The third research question was whether or not feelings of awe and subsequent gratitude contribute to participants' well-being, as awe was suggested to increase well-being and personal change (45) and to be related to openness and extroversion as a personality structure (46). In our study, Awe/Gratitude was indeed moderately associated with well-being and would predict 9% of participants' well-being variance. Best predictors of participants' emotional well-being were multidimensional life satisfaction and low perceived burden (related to the pandemic), and further Awe/Gratitude and *Nature/Silence/Contemplation*. Thus, these perceptions have their role in relation to well-being, but not in the forefront.

Even when it is true that Awe/Gratitude facilitates to be more aware of positive changes in attitudes and behaviors due to the COVID-19 pandemic, it, nevertheless, does not relevantly buffer against the perceived burdens and restrictions as the associations are marginal only. Moderator analyses further indicated that Awe/Gratitude was not a significant moderator of the link between perceived changes and well-being. It cannot be called a buffering resilience factor, but rather an ability to perceive the positive aspects in life—in spite of the stressors. Actually, this could be considered an interesting process of inner development similar or closely related to the concept of mindfulness: being aware of the situation as it is, and deal with the situation as it is without judgment, as judgmental processes would result in negative emotions (47–49).

The results show that the practice of meditation and praying is related to Awe/Gratitude and (in terms of training) may sensitize to be more aware of the underlying moments and situations that cause feelings of wondering awe, and thus, it was of interest whether well-being could moderate these pathways. We found that the effect of both spiritual practices (meditation and praying), when moderated by a person's well-being, increases the levels of Awe/Gratitude more than if they were evaluated separately, while the interaction between more intense *Relationship* and well-being decreases Awe/Gratitude scores. This result could be due to a range of participants who reported lower well-being but high scores for perceived changes in terms of more intense *Relationship* (which may become more relevant as a stabilizing resource). The variables with the strongest contribution to higher levels of Awe/Gratitude were perceived changes in *Relationships* and well-being, and the strongest moderation was observed between frequency of meditation practices and well-being. Praying as a separate variable did not contribute to the model.

Limitations

We are aware that the data are not representative for all parts of German society, as the recruitment process may have favored persons with Internet access, academic contexts, and persons with a Christian background. However, while this selection bias is acceptable to address the research questions, it would be interesting to analyze persons from others contexts.

Due to the cross-sectional design of the study, no causal conclusions can be drawn. To account for this, we added data from different recruitment months (resulting in different cohorts). Data from these cohorts (**Figure 3**) indicate that a decrease in well-being and Awe/Gratitude may precede an increase in perceived burden. However, one cannot fully exclude the possibility that perceptions of Awe are better triggered during spring times instead of late autumn.

CONCLUSIONS

Perceptions of Awe and subsequent Gratitude are higher in persons with a religious background (11), and in those with more intense meditation or prayer practice. Such spiritual practices may facilitate these perceptions in terms of "training" and attitude. However, these experiences of Awe and Gratitude do not usually buffer against adverse events in life and cannot prevent perceived burden due to the pandemic; rather, they facilitate to, nevertheless, perceive the positive aspects of life, particularly *Nature/Silence/Contemplation*, *Spirituality*, and *Relationships*. This indicates higher awareness of a connectedness with the world around and with concrete others (horizontal direction of relations) and with the Sacred (vertical direction of relations). As Awe/Gratitude is further mediating the effects of *Nature/Silence/Contemplation* on well-being, intervention programs to train these perceptions could be considered in order to support people particularly in the time of the COVID-19 pandemic, as these self-transcendent feelings are also related to prosocial behaviors with respectful treatment of others and commitment to persons in need (17).

DATA AVAILABILITY STATEMENT

According to the data protection regulations, the data set cannot be made publicly available. Data are however available from the first author upon reasonable request.

ETHICS STATEMENT

Ethical review and approval was not required for the study on healthy human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Participants were assured confidentially and were informed about the purpose of the study and data protection information at the starting page of the online survey. By filling in the anonymous questionnaire, interested persons consented to participate.

AUTHOR CONTRIBUTIONS

AB designed the study, set up the online survey, and wrote the first draft of the paper. DR and AB undertook the statistical analyses. KB and JS were actively involved in writing and revising the manuscript. All authors provided feedback and approved the final manuscript.

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Family Resilience, Parenting Styles and Psychosocial Adjustment of Children With Chronic Illness: A Cross-Sectional Study

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Objectives: To evaluate the level of parent-reported family resilience, parenting styles and psychosocial adjustment of children with chronic illness and to identify the relationships between family resilience, parenting styles and psychosocial adjustment in families with children with chronic illness.

Methods: A cross-sectional study was conducted between June 2019 and August 2019. A total of 236 parents of children with chronic illness and 98 parents with healthy children were recruited from general hospitals by convenience sampling. A parent completed the Chinese Family Resilience Assessment Scale, the Parenting Rearing Patterns Questionnaire and the Strengths and Difficulties Questionnaire. Family resilience, parenting styles, and psychosocial adjustment of children with chronic illness were compared with those of healthy children. Structural Equation Modeling (SEM) was performed to explore the mediation effect of parenting styles between family resilience and psychosocial adjustment among children with chronic illness.

Results: Parents of children with chronic illness reported lower level of family resilience and authoritative parenting, but more peer relationship problems compared to parents of healthy children. SEM showed that authoritative parenting fully mediated the relationship between family resilience and psychosocial adjustment of children with chronic illness.

Conclusion: Childhood chronic illness reduces family resilience, authoritative parenting and children's psychosocial adjustment, but authoritative parenting mediated these effects, so authoritative parenting may be important for family resilience in families of children with chronic illness. Pediatric clinicians and nurses should provide family-centered interventions, as well as parenting training, to improve children's psychosocial outcomes.

Keywords: family resilience, parenting styles, psychosocial adjustment, mediating effect, children with chronic illness

INTRODUCTION

It has been reported that 10–20% of children in China suffered from chronic illness, and the prevalence of childhood chronic illness will reach to 29.4‰ by 2020 (1). Chronic illness is a physical or mental condition, which is defined as a process of 'long duration and generally slow progression that requires ongoing management over a period of years or decades' (2).Such conditions include diabetes, chronic kidney disease, congenital heart disease, bone/joint disorders, genetic disorders and et al., which are rarely cured completely (2, 3), and are severe challenges to the children and their families (4). In this study, chronic illnesses included endocrine system diseases, neurological developmental diseases, rheumatic system diseases, congenital heart disease, chronic kidney disease and cancers.

The incidence of psychological problems, such as poor social initiative problems, reluctance to participate in group activities, and internalizing problems such as anxiety, depression and social withdrawal was reported to be as high as 21.9% in children and adolescents with chronic illness (5, 6). Meanwhile, childhood chronic illness has also been consistently reported to be correlated with decreased quality of life of family members and impaired family function (7–10).

Despite the above mentioned negative impacts of childhood chronic illness, there is also evidence that some families with children with chronic illness, including mental, emotional, and behavioral disorders (11), pediatric asthma (12), type 1 diabetes (13) and pediatric cancer (14) demonstrate family strength to positively cope with the challenge of chronic illness (15, 16), and take advantage of their stressful experiences to develop stronger relationships, better family cohesion, and positive family belief systems (17, 18).

Walsh (19) defined the family system's capacity to withstand and rebound from adversity, to become stronger and more resourceful as "family resilience." Family resilience involves there being shared family belief systems, family organizational processes and shared family communication or problems solving processes. Families of children with mental, emotional and behavior disorders can sometimes be more resilient than families in the general population (11). However, family resilience among Chinese families of children with chronic illness remained less studied.

Family resilience may play a significant role in children's psychosocial adjustment, being for instance positively correlated with children's prosocial behavior (20). Family resilience may also mitigate the harmful effects of adverse childhood experience on children's behavioral outcomes (21), while family functioning may be negatively correlated with children's depressive symptoms (22), and positively related to better child adjustment with fewer externalizing problems and less behavioral acting out, as well-greater social competence (14). Family function may be one of the key aspects of family resilience (23), but the relationship between family resilience and child adjustment has not been widely studied. Some studies even propose that family resilience does not necessarily ensure children's psychosocial adjustment, for some children still present with anxiety, depression, learning disabilities and behavior or conduct problems (11). One possible explanation for the differences is the varied measures of family resilience used in previous studies. Therefore, it is necessary to further explore the role of family resilience in the psychosocial adjustment of children with chronic illness.

Here, we chose to use the Chinese Family Resilience Assessment Scale because based on Belsky's (24) process of parenting model. Taraban and Shaw (25) developed an updated process of parenting model, creating broad categories to represent "Family Social Environment," "Parental Characteristics" and "Child Characteristics," which supported the interactive associations among family social contextual factors, parents and children. In this model, the influence of the family social environment on child characteristics may be traced back to parenting styles. Therefore, family resilience may interact with family parenting style to affect management of the child's condition, in turn affecting the child's growth and development. Regarding parenting style, Baumrind (26) identified three styles: permissive (few rules or restrictions), authoritarian (harsh and hostile), and authoritative (democratic and warm) (27). Since, a fourth style is generally included; inconsistent parenting, which is sometimes permissive and sometimes harsh and hostile (28).

Parenting style may be affected by stressful life events occurring within families (21), which may result in unhealthy parental emotions that contribute to an increase in inappropriate parenting practices (29–31). In a sample of Latino Youth, authoritative parenting usually occurred within highly cohesive family systems, while authoritarian parenting usually occurred within less cohesive family systems (32). Family resilience may also be related to parental coping and parental emotional support (11). However, the details of the relationship between family resilience and parenting styles remain unexplored. Positive parenting, including authoritative parenting, is predictive of child resilience, self-esteem and life satisfaction (33, 34), while inconsistent parenting may make children aggressive, hostile, opposed, anxious and depressed (35–37). However, the relationship between family resilience, parenting styles and psychological adjustment of children with chronic illness is not well-characterized in contemporary literature.

Understanding the relationships between the psychosocial adjustment of children with chronic illness, family resilience and parenting styles would help to develop interventions to improve the psychosocial well-being of children with chronic illness and their families. This study therefore collected data on parenting style, family resilience and psychosocial adjustment of the child with chronic illness. We hypothesized that (1) families with children of chronic illness would be less resilient, less likely to adopt positive parenting styles, and having children with more psychological and behavioral problems compared to those with healthy children; (2) parenting styles would mediate the relationship between family resilience and the psychosocial adjustment of children with chronic illness.

METHODS

Participants

A total of 334 parents (236 with children diagnosed of chronic illness, 98 with healthy children) were enrolled in this study. The inclusion criteria for parents of children with chronic illness were: (1) at least having one child aged between 3 and 16 years old with a medically diagnosed uncured chronic illness that had lasted at least 3 months continuously (38); (2) parents aged ≥18 years. Inclusion criteria for the healthy control group were having children never being diagnosed with any chronic health condition. Parents with impaired cognitive function or severe medical conditions as diagnosed by a physician were excluded. Families were also excluded if the target parent and child or any other family member had been diagnosed by a physician as having a history of psychiatric illness or reported currently taking antipsychotic medication. Families including any member with a serious physical or mental illness were also excluded.

Procedures

This study was approved by the Institutional Ethics Committee of the Medical University (No. 2019017), in accordance with the Declaration of Helsinki. A convenience sampling method was used to collect data between June 2019 and August 2019 from general hospitals in three cities in China (Wenzhou, Ningbo and Shanghai). Parents of children with chronic illness were recruited from the outpatient and inpatient department of the general hospitals. Potential participants were approached by a member of the research team, either in the pediatric outpatient waiting rooms, or in the pediatric inpatient wards of the hospital. In order to ensure that the healthy controls were from similar communities, parents of healthy children were recruited from the medical examination centers of the same hospitals while waiting for their children's annual routine physical examinations. Only one parent per family was interviewed. After screening according to the exclusion criteria and informed consent, all the participants completed a survey questionnaire in a designated room. Data was collected by members of the research team after training from the first author. The entire survey process lasted about 20–30 min, and all participants were provided with a small gift of a plush toy or keychain valued at $2 as compensation. Of the 262 parents of children with chronic illness who agreed to participate, 236 (90.08%) participants returned the complete questionnaire. Of the 108 parents of healthy children who consented to participate, 10 participants were excluded due to incomplete answers, resulting in a valid sample size of 98 (90.74%).

MEASURES

Chinese Family Resilience Assessment Scale

The Family Resilience Assessment Scale, developed by Sixbey (39), was adapted to Chinese culture by Dong et al. (40). The 44-item C-FRAS contains four subscales: family communication and problem solving (27 items); utilizing social and economic resources (eight items); maintaining a positive outlook (six items); ability to make meaning of adversity (three items). Answers to individual items use Likert four-point scales from 1 = strongly disagree to 4 = strongly agree, producing a total score between 44 and 176. Higher scored indicate higher levels of family resilience. Here, Cronbach's α was 0.970, which indicates excellent reliability.

Parenting Rearing Patterns Questionnaire

Parenting styles were assessed using the Parenting Rearing Patterns Questionnaire (41). It is a 28-item questionnaire with four dimensions: authoritative parenting (10 items); permissive parenting (seven items); authoritarian parenting (three items); and inconsistent parenting (eight items). Answers are scored on five-point scale from 1 (very inconsistent) to 5 (very consistent). The Cronbach's α in the present study was 0.787, which indicates acceptable reliability.

Strengths and Difficulties Questionnaire

Children's psychosocial adjustment, was assessed by the Strengths and Difficulties Questionnaire (SDQ; (42)). SDQ is a structured questionnaire to screen psychiatric problems of children and adolescents, and parallel versions of the SDQ are available for completion by children's parents, teachers, and children themselves (43). The parent version of SDQ, suitable for children aged 3 to 16 years, was used in this study. It is a 25-item scale with five subscales, including emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behavior. All items were scored on a three-point scale 0 to 2 (0, "not true;" 1, "somewhat true;" 2, "certainly true"). The first four subscales (20 items) are summed to generate the total difficulties score ranging from 0 to 40, with higher scores representing a higher degree of difficulties. The last subscale (five items) belongs to the strength questionnaire with total score ranging from 0 to 10. The higher score in the last subscale indicates a higher degree of prosocial behaviors (44). The Cronbach's α in the present study was 0.728, which indicates acceptable reliability.

Statistical Analysis

Descriptive data were presented as Mean ± SD or frequency (percentage). *T*-tests were conducted to compare the children with chronic illness to the control healthy children. Pearson correlations were calculated to examine the unadjusted correlations between family resilience, parenting styles and psychological adjustment among children with chronic illness, and the SEM (Structural Equation Modeling) was employed to test the mediating effect of parenting styles between family resilience and Children's psychosocial adjustment. The maximum likelihood method was used to construct the model. Chi-square/degrees of freedom (χ2/df), root mean square approximation error (RMSEA), Cumulative Fit Index (CFI), Tucker-Lewis index (TLI) and Incremental Fit Index (IFI) were used to estimate the fit of the model. The model was proved to have a good fit if $\chi^2/\mathrm{df} < 3$, RMSEA < 0.08, SRMR < 0.05, as well as CFI, TLI and IFI > 0.9 (45). Analysis of data was carried out using SPSS Version 25.0 (IBM Corp., Armonk, NY, USA) and Amos 25.0 programs (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered significant.

RESULTS

Demographic Characteristics

Of the 236 parents of children with chronic illness, 59 were fathers and 177 were mothers, mean age 37.48 ± 6.58 years. Of the 98 parents of healthy children, 24 were fathers and 74 were mothers, mean age 36.78 ± 7.44 years. Children with chronic illness (148 male, 88 female) had a mean age of 8.69 ± 3.62 years, while healthy children (49 male, 49 female) had a mean age of 7.42 ± 3.09 years. Thirty-seven children (15.7%) were diagnosed with endocrine system diseases, including type 1 diabetes mellitus and growth hormone deficits, 12 (5%) with

TABLE 1 | Demographic characteristic of families of children with chronic illness and families of healthy children.

Variable	Families of children with chronic illness (*n* = 236) Mean ± SD, (*N*) %	Families of healthy children (*n* = 98) Mean ± SD, (*N*) %	t/χ^2	*p*-value
Parent Age	37.48 ± 6.576	36.78 ± 7.441	-0.856^{Δ}	0.393
Parent gender				
Male	25% (59)	24.5% (24)	0.01	0.922
Female	75% (177)	75.5% (74)		
Parent occupational status				
Employed	59.3% (140)	70.4% (69)	3.634	0.057
Unemployed	40.7% (96)	29.6% (29)		
Parent education level				
Middle School and below	53.8% (127)	32.7% (32)	21.539	0.000
High School/secondary school	19.5% (46)	14.3% (14)		
College or higher	26.7% (63)	53.0% (52)		
Monthly household income				
<3000RMB	17.4% (41)	12.2% (12)	15.587	0.001
3000–5000RMB	28.0% (66)	14.3% (14)		
5001–8000RMB	25.8% (61)	23.5% (23)		
>8000RMB	28.8% (68)	50% (49)		
The number of children				
one	29.7% (70)	48% (47)	10.187	0.001
two or more	70.3% (166)	52% (51)		
Child Age				
3–6 year	34.3% (81)	45.9% (45)	5.828	0.054
7–12 year	49.6% (117)	45.9% (45)		
13–16 year	16.1% (38)	8.2% (8)		
Child gender				
Male	62.7% (148)	50% (49)	4.625	0.032
Female	37.3% (88)	50% (49)		
Types of chronic illness				
Endocrine system (Type 1 diabetes mellitus/Growth hormone deficits)	15.7% (37)	–	–	–
Nervous system (Cerebral palsy/Multiple sclerosis)	5% (12)	–		
Rheumatic system (Juvenile idiopathic arthritis/Allergic purpura/Systemic lupus erythematosus/Kawasaki disease)	29.2% (69)	–		
Cardiovascular system (Congenital heart disease)	6.8% (16)	–		
Chronic kidney disease	22.5% (53)	–		
Cancer (Leukemia/Malignancies)	10.6% (25)	–		
Others	10.2% (24)	–		
Sources of medical expenses				
Self-paying	44.1% (104)	38.8% (38)	0.794	0.373
Medicare	55.9% (132)	61.2% (60)		

SD, standard deviation; $^{\Delta}$*, t value.*

TABLE 2 | Differences in family resilience, parenting styles and child psychosocial adjustment by childhood chronic illness history ($n = 334$).

	Children with chronic illness ($n = 236$)	Healthy children ($n = 98$)	*t*	*p*-value
Family resilience	127.82 ± 9.942	135.27 ± 16.154	4.240	0.000
FCPS	80.66 ± 7.085	84.90 ± 10.305	3.721	0.000
USER	21.44 ± 2.626	22.69 ± 3.565	3.133	0.002
MPA	16.91 ± 2.044	18.43 ± 2.306	5.962	0.000
AMMA	8.81 ± 1.003	9.24 ± 1.347	3.252	0.001
Authoritative parenting	37.44 ± 5.919	39.20 ± 5.183	2.574	0.010
Permissive parenting	22.45 ± 5.471	23.54 ± 5.449	1.662	0.097
Authoritarian parenting	8.83 ± 2.041	8.40 ± 2.389	−1.570	0.118
Inconsistent parenting	23.98 ± 4.941	24.46 ± 6.292	0.668	0.505
Emotional symptoms	2.80 ± 2.021	3.15 ± 2.198	1.430	0.154
Conduct problems	2.16 ± 1.456	2.35 ± 1.386	1.078	0.282
Hyperactivity/inattention	4.39 ± 2.046	4.46 ± 2.188	0.293	0.770
Peer relationship problems	3.36 ± 1.649	2.94 ± 1.545	−2.188	0.029
Prosocial behavior	6.31 ± 2.365	6.38 ± 2.147	0.262	0.794
Total difficulties scores	12.71 ± 4.824	12.90 ± 5.142	0.322	0.748

FCPS, Family Communication and Problem Solving; USER, Utilizing Social and Economic Resources; MPA, Maintaining a Positive Attitude; AMMA, Ability to Make Meaning of Adversity.

nervous system diseases, including cerebral palsy and multiple sclerosis, 69 (29.2%) with rheumatic system diseases, including juvenile idiopathic arthritis, allergic purpura and systemic lupus erythematosus, 16 (6.8%) with congenital heart disease, 53 (22.5%) with chronic kidney disease, 25 (10.6%) with cancers and 24 (10.2%) with other diseases. The demographic characteristics of the participants and their children were summarized in **Table 1**. There was no difference between two groups in the parents' age, gender, employment status, children's age and medical insurance. However, the childhood chronic illness group tended to have parents with lower education ($\chi^2 = 21.539$, $p = 0.000$), families with more children ($\chi^2 = 10.187$, $p = 0.001$), lower monthly household income ($\chi^2 = 15.587$, $p = 0.001$) and more male children ($\chi^2 = 4.625$, $p = 0.032$), see **Table 1**.

Family Resilience, Parenting Styles and Psychosocial Adjustment of Children With Chronic Illness

As shown in **Table 2**, parents of children with chronic illness scored lower on family resilience and its subscales ($p < 0.05$), and lower on authoritative parenting style ($p = 0.010$) compared to the parents of healthy children. The psychosocial adjustment of children with chronic illness was similar to that of healthy children, except that parents of children with chronic illness reported more their children had more peer relationship problems than parents of healthy children ($p = 0.029$).

Relationship of Family Resilience, Parenting Styles and Psychosocial Adjustment of Children With Chronic Illness

The results of the correlation analysis were shown in **Table 3**. Family resilience was positively correlated with authoritative parenting ($r = 0.278$, $p < 0.01$) and authoritarian parenting ($r = 0.190$, $p < 0.01$), but negatively correlated with inconsistent parenting ($r = -0.169$, $p < 0.01$). Family resilience was positively related to prosocial behavior ($r = 0.139$, $p < 0.05$) and negatively related to total difficulties ($r = -0.147$, $p < 0.05$). Authoritative parenting was negatively correlated to the total difficulties ($r = -0.238$, $p < 0.01$) and positively correlated to the prosocial behaviors ($r = 0.326$, $p < 0.01$).

Mediating Effect of Authoritative Parenting Between Family Resilience and Psychosocial Adjustment Among Children With Chronic Illness

Based on the results of the correlation analysis, it was hypothesized that authoritative parenting would mediate between family resilience and psychosocial adjustment. SEM was employed to test the model, with family resilience as the independent variable, total difficulties and prosocial behavior as dependent variables, and authoritative parenting as the mediating variable. SEM indicated that the measurement model had an acceptable fit to the data, with $x^2/df = 1.565$; CFI = 0.941; TLI = 0.913; IFI = 0.944; SRMR = 0.0483, and RMSEA = 0.049.

The bootstrap bias-corrected estimator was used to further test the above model. As shown in **Tables 4**, **5** and **Figure 1**, the standardized path coefficients supported the positive correlation with family resilience and authoritative parenting style ($\beta = 4.552$, SE = 1.029, $p < 0.001$), the positive correlation with family resilience and prosocial behavior ($\beta = 0.322$, SE = 0.357, $p = 0.366$), and the negative correlation with family resilience and total difficulties ($\beta = -0.133$, SE = 0.141, $p = 0.346$). The 95% bias-corrected confidence intervals (CIs) for the direct effect from family resilience to the total difficulties was −0.304 to 0.146, including zero in the 95% CI, indicating that the direct effect was not significant. The 95% CIs for indirect effect from family resilience to the total difficulties via authoritative parenting style was −0.239 to −0.044, and the 95% CIs for the indirect effect from family resilience to prosocial behavior was 0.067–0.216. The 95% CIs did not include zero, indicating the existence of a full mediating effect of authoritative parenting style between family resilience and psychosocial adjustment of children with chronic illness.

DISCUSSION

The purpose of this study was to investigate the family resilience, parenting styles and psychosocial adjustment of children with chronic illness and to explore their relationships from the perspectives of parents.

The present study found that parents of children with chronic illness reported lower level of family resilience compared to parents of healthy children. This result suggested that being diagnosed with childhood chronic illness is a stressful event that might weaken the ability of family as a whole to accommodate stressful events together (46–48). Parents of children with chronic illness also reported lower scores on the authoritative parenting compared to their counterparts in present study, which partially support the result of previous study that parents of children with chronic illness tended to be over-involved in children's lives, and their children were more likely to depend on their parents without autonomy (49). Children with chronic illness were reported to have more peer relationship problems compared to healthy children in the present study, which indicates that children with chronic illness might be less capable of dealing with peer relationship problems (50).

As Chinese culture emphasizes interdependence and emotional restraint to maintain harmonious interpersonal relationships (51), our results suggest that authoritarian parenting was positively correlated with family communication and problem solving and total score of family resilience. However, authoritarian parenting did not significantly correlate with any child behavior outcomes in this study. A possible explanation is that children's authoritarian parenting is normal within Chinese culture (52). The permissive parenting style was not significantly correlated with family resilience, but was positively related to total difficulties and weaker prosocial behaviors, which is in consistent with previous research (53–56). Permissive parenting provides minimal structure (57), so may have little influence on how family subsystems interact with one another in terms of their cohesion and flexibility to cope with childhood chronic illness. In the present study, authoritative parenting style was negatively correlated with total difficulties and positively correlated with prosocial behavior among children with chronic illness, as found in previous studies (58, 59), suggesting that authoritative parenting is the most effective parenting style to provide a supportive context for child development (60), possibly providing greater family cohesion and more balanced family functioning (61).

Family resilience was negatively correlated with total difficulties and positively correlated with prosocial behavior, as found previously (62–64). Furthermore, in line with our hypothesis, the present study found that authoritative parenting

TABLE 3 | Correlation analysis between family resilience, parenting styles and psychosocial adjustment of children with chronic illness ($n = 236$).

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1.FCPS	1													
2.USER	0.370**	1												
3.MPO	0.435**	0.249**	1											
4.AMMA	0.348**	0.202**	0.377**	1										
5.Family resilience	0.935**	0.599**	0.619**	0.480**	1									
6.Authoritative	0.317**	0.096	0.015	0.237**	0.278**	1								
7.Permissive	0.038	−0.081	0.003	−0.091	−0.003	0.117	1							
8.Authoritarian	0.194**	0.097	0.100	0.059	0.190**	0.150*	0.223**	1						
9.Inconsistency	−0.143*	−0.087	−0.156*	−0.120	−0.169**	−0.054	0.158*	0.206**	1					
10.Emotional symptoms	−0.060	−0.078	−0.114	−0.095	−0.096	−0.064	0.077	0.032	0.066	1				
11.Conduct problems	−0.038	0.037	−0.022	−0.084	−0.030	−0.239**	0.166**	0.046	0.086	0.295**	1			
12.Hyperactivity/inattention	−0.125	−0.054	−0.090	−0.095	−0.132*	−0.211**	0.067	−0.081	0.157*	0.289**	0.478**	1		
13.Peer relationship problems	−0.141*	0.017	−0.081	−0.081	−0.121	−0.145*	0.060	0.034	−0.057	0.283**	0.179**	0.067	1	
14.Prosocial behavior	0.130*	0.095	0.057	0.095	0.139*	0.326**	−0.170**	0.080	−0.065	−0.057	−0.372**	−0.368**	−0.201**	1
15.Difficulties total scores	−0.138*	−0.039	−0.120*	−0.133*	−0.147*	−0.238**	0.131*	−0.004	0.101	0.727**	0.689**	0.712**	0.543**	−0.361**

FCPS, Family Communication and Problem Solving; USER, Utilizing Social and Economic Resources; MPA, Maintaining a Positive Attitude; AMMA, Ability to Make Meaning of Adversity; *$P < 0.05$, **$P < 0.01$.

TABLE 4 | The model path diagram for family resilience, authoritative parenting and psychosocial adjustment of children with chronic illness.

Variables	Unstandardized coefficients	Standardized coefficients	S.E.	*T*	*p*
Family resilience → Authoritative parenting	4.552	0.416	1.029	4.424	***
Authoritative parenting → Total difficulties	−0.035	−0.281	0.013	−2.741	0.006
Family resilience → Total difficulties	−0.133	−0.097	0.141	−0.943	0.346
Authoritative parenting → Prosocial behavior	0.119	0.298	0.029	4.251	***
Family resilience → Prosocial behavior	0.322	0.068	0.357	0.904	0.366

****P < 0.001.*

TABLE 5 | Intermediate, direct, and total effect analysis of authoritative parenting in the family resilience and psychosocial adjustment.

	Path	Effect size	Bias-corrected 95%CI		Effect proportion (%)
			Lower	Upper	
Dependent variable: total difficulties					
	Mediating effect	−0.117	−0.239	−0.044	54.67
	Direct effect	−0.097	−0.304	0.146	45.32
	Total effect	−0.214	−0.398	0.000	
Dependent variable: prosocial behavior					
	Mediating effect	0.124	0.067	0.216	62.63
	Direct effect	0.074	−0.081	0.234	37.37
	Total effect	0.198	−0.052	0.349	

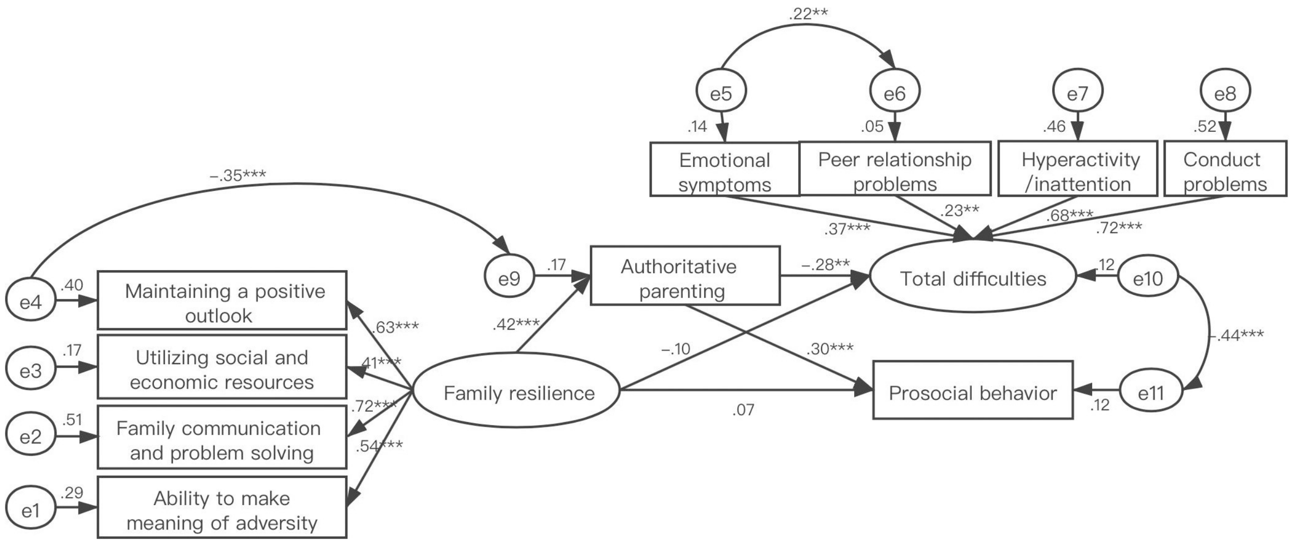

FIGURE 1 | Structural equation model of family resilience, authoritative parenting and psychosocial adjustment. Types of chronic illness as control variable.

played a fully mediating role between family resilience and child psychosocial adjustment (both total difficulties and prosocial behavior). This result provides evidence that parenting may be affected by having a child with chronic illness and that the family's perceived ability to cope with the adversity of chronic illness is related to authoritative parenting practices which positively affect the child's emotional and behavioral health (25). Families with high levels of resilience have flexibility in patterns of family organization that enable the family system to hold together in times of crisis, rapidly mobilize crisis management skills, develop new abilities and stronger bonds (65), communicate openly and effectively with their children and maintain close family relationships, which would contribute to positive parenting to affect children's psychosocial adjustment (32).

The mediation analysis helps to clarify that family resilience impacts children's psychological adjustment through authoritative parenting. On basis of these findings, clinicians should conduct family-based surveys and in-depth interviews in future studies to guarantee contact with parents and to obtain valuable information about family variables pertaining to the children's mental health. The focus should be on the link between parenting styles and the children's psychosocial adjustment, providing parents with information about the benefits and recommendations of authoritative parenting styles, and encouraging authoritative parenting as a method of developing family resilience. It is hoped that the development and implementation of such targeted interventions will ultimately improve the psychosocial adjustment of children with chronic illnesses and their families.

Limitations

This study also has some limitations. First, the cross-sectional design of this study cannot determine the causality relations among the variables. It is necessary for the future studies to employ a longitudinal design to test the mediating models. Additionally, all the questionnaires were filled out by one parent, which may have introduced individual positivity bias across all three questionnaires. Also, the point of view of the children was not investigated. Therefore, the future studies can explore family resilience, parenting styles and psychosocial adjustment focusing on parent-child dyads. Third, there should be with caution about the generalizability of the results of this study since our sample was obtained from general hospitals in three cities of eastern China using convenience sampling and the sample size was modest. Fourth, the severity of the childhood chronic illnesses was not considered in the analysis, which limits the interpretation of the findings.

CONCLUSION

Parents of children with chronic illnesses reported that their children had higher levels of psychosocial problems and that the family was less resilient. However, parents who scored higher on authoritative parenting reported more resilience and fewer psychosocial problems for their children. Moreover, authoritative parenting appeared to account for much of the relationship between family resilience and improved child functioning, suggesting that education on parenting style would be helpful for families of children with chronic illness.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of Medical University (No. 2019017). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YQ: data collection, writing - original draft, writing review, and editing. LX, YP, CH, YH, and HX: data collection, data curation, writing review, and editing. ZL: conceptualization, writing review, and editing. CD: conceptualization, writing - original draft, writing review, and editing. All listed authors meet the authorship criteria and were in agreement with the content of the manuscript.

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A Structural Equation Model of Health-Related Quality of Life in Chinese Patients With Rheumatoid Arthritis

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Background: The aim of this study was to examine how body image, Disease Activity Score in 28 joints, the feeling of being anxious, depression, fatigue, quality of sleep, and pain influence the quality of life (QoL) in patients with rheumatoid arthritis (RA).

Methods: A multicenter cross-sectional survey with convenience sampling was conducted from March 2019 and December 2019, 603 patients with RA from five hospitals were evaluated using the Body Image Disturbance Questionnaire, Disease Activity Score in 28 joints, Hospital Anxiety and Depression Scale, Fatigue Severity Scale, Pittsburgh Sleep Quality Index, Short Form 36 Health Survey, and Global Pain Scale. The relationship between quality of life and other variables was evaluated by using the structural equation model (SEM).

Results: A total of 580 patients were recruited. SEM fitted the data very well with a root mean square error of approximation (RMSEA) of 0.072. Comparative fit index of 0.966, and Tucker-Lewis index of 0.936. The symptoms and the normalized factor load of six variables showed that the normalized factor load of pain was 0.99.

Conclusions: The QoL model was used to fit an SEM to systematically verify and analyze the population disease data, biological factors, and the direct and indirect effects of the symptom group on the QoL, and the interactions between the symptoms. Therefore, the diagnosis, treatment and rehabilitation of RA is a long-term, dynamic, and complex practical process. Patients' personal symptoms, needs, and experiences also vary greatly. Comprehensive assessment of patients' symptoms, needs, and experiences, as well as the role of social support cannot be ignored, which can help to meet patients' nursing needs, improve their mood and pain-based symptom management, and ultimately improve patients' QoL.

Keywords: rheumatoid arthritis, quality of life, body image, pain, depression

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that may cause cartilage and bone damage, as well as significant disability (1). RA usually involves the small joints in the hands and feet and is characterized by joint pain, joint swelling, and synovial joint destruction (2). Its prevalence in adults in the USA and Europe is ∼0.42–1.25% and 0.28–0.45% in China (3, 4).

Individuals with RA frequently report reduced health-related quality of life (HRQoL), which is an indicator of the impact of one's health on his/her physical, emotional, and social well-being (5). RA is very painful and affects the social activities of the patient. Many patients have been sick since childhood, this painful experience may be associated with psychosocial impairment and may influence the negative outcomes in RA (6). Patients with RA show systemic symptoms, such as pain, stiffness, muscle weakness, fatigue, and joint swelling; all of these might cause irreversible destruction of joints or deformities accompanied by physical disability when the disease progresses; all of the abovementioned symptoms are the most common causes of continual pain and impaired functioning (7), and significantly decrease a person's mobility, productivity, and QoL (8, 9).

Pain is the symptom that the patient feels most directly. RA patients also have a higher incidence of depression (10). More than half of the patients experience fatigue. Fatigue is described as either physical or mental fatigue, which combined may lead to disability. Patients feel tired, depressed, or frustrated, and are unable to complete their daily tasks (11, 12). Fatigue had a substantial influence on the patients' lives, while pain was the dominant factor in the fatigue experience and degree (13). Poor sleep quality is common in patients with RA and may lead to disease aggravation and decreased HRQoL. The prevalence of body image disturbance (BID) is 24.2%, and poor social functioning and anxiety are also present (14). Besides, increasing disease severity has been associated with worsening disability, pain, fatigue, QoL, and work and activity impairment (15).

Moreover, RA is related to reverse characteristics in terms of demographics, clinical features, as well as psychological status. An uncertain future concerning physical ability, work and employment status, family responsibilities, and social activities can be difficult to face, especially in individuals with RA. RA patients are at higher risk of developing comorbidities (16), which are also associated with advanced age. In China, patients with RA have a similar prevalence of comorbidities when compared to those in other Asian countries. Advanced age and long disease duration are possible risk factors for comorbidities, which may increase mortality and affect treatment strategies, resulting in worse outcomes (17, 18). Patients with RA tend to have a higher risk for many comorbidities (19, 20).

Improving patients' symptoms can improve their quality of life. Depression is a major determinant of functional capacity in RA (21). Effective social support may relieve patients' fatigue, which is related to patients' disease activity and QoL (22).

Many studies have considered a simple associative relationship between two of the following variables or have evaluated the variables as a single item instead of one with multiple dimensions (23–25): pain, fatigue, depression, sleep quality, and QoL impact. There has been no systematic and comprehensive analysis of the relationship between patients' demographic data and symptoms, and the causal relationship between RA symptoms and QoL. It is possible to evaluate and manage patients comprehensively and provide a theoretical basis to formulate appropriate objective interventions to improve QoL.

However, improving the quality of life does not always accompany QoL improvement. Physical aspects are commonly evaluated as most important and are related to a patient's physical condition only as a consequence of illness and treatment.

The framework of this study is derived from QoL research; the current challenge is to devise a model to clarify the elements of HRQoL and relationships among them. Wilson and Cleary have suggested specific causal relationships between health concepts encompassing biological, social, and psychological variables (**Figure 1**) (26).

A linear progression without dominant reciprocal effects or links between nonadjacent concepts has been proposed. Wilson and Cleary's model outlines potential causal relationships between the variables that play a major role in the origins of HRQoL.

Based on the above rationale, we aimed to: (1) describe the current status of HRQoL in patients with RA, including parameters such as gender socioeconomic status, and disease characteristics and explore their relevance; (2) perform an exploratory analysis of relevant parameters including the effects of pain, fatigue, and physical image disorders, depression, sleep quality, disease activity, HRQoL, and the interaction between multiple variables; (3) assess HRQoL and determine which factors, based on the Wilson and Cleary model, contribute to the prediction of HRQoL among patients with RA; and (4) estimate the potential impact of success on RA-HRQoL to provide a theoretical basis for effective interventions against identified factors.

MATERIALS AND METHODS

Study Design and Patient Recruitment

A multicenter cross-sectional study with a convenience sampling method was conducted. Patients with RA were recruited from five hospitals between March 2019 and December 2019. The inclusion criteria included RA diagnosis according to the American Rheumatism Association 1987 revised criteria, age ≥18 years, able to interact in Chinese efficiently, and willing to provide written informed consent. People who have cognitive impairment or current severe diseases, such as cancer and stroke, were not included.

Abbreviations: QoL, quality of life; SEM, structural equation modeling; RMSEA, root mean square error of approximation; HRQoL, health-related quality of life; RA, rheumatoid arthritis; BID, body image disturbance; DAS28, Disease Activity Score in 28 joints; SF-36, Short Form 36 Health Survey; PCS, physical components summary; MCS, mental components summary; SSRS, Social Support Rating Scale; SD, standard deviation; IQR, interquartile range; RMB, renminbi; BMI, body mass index.

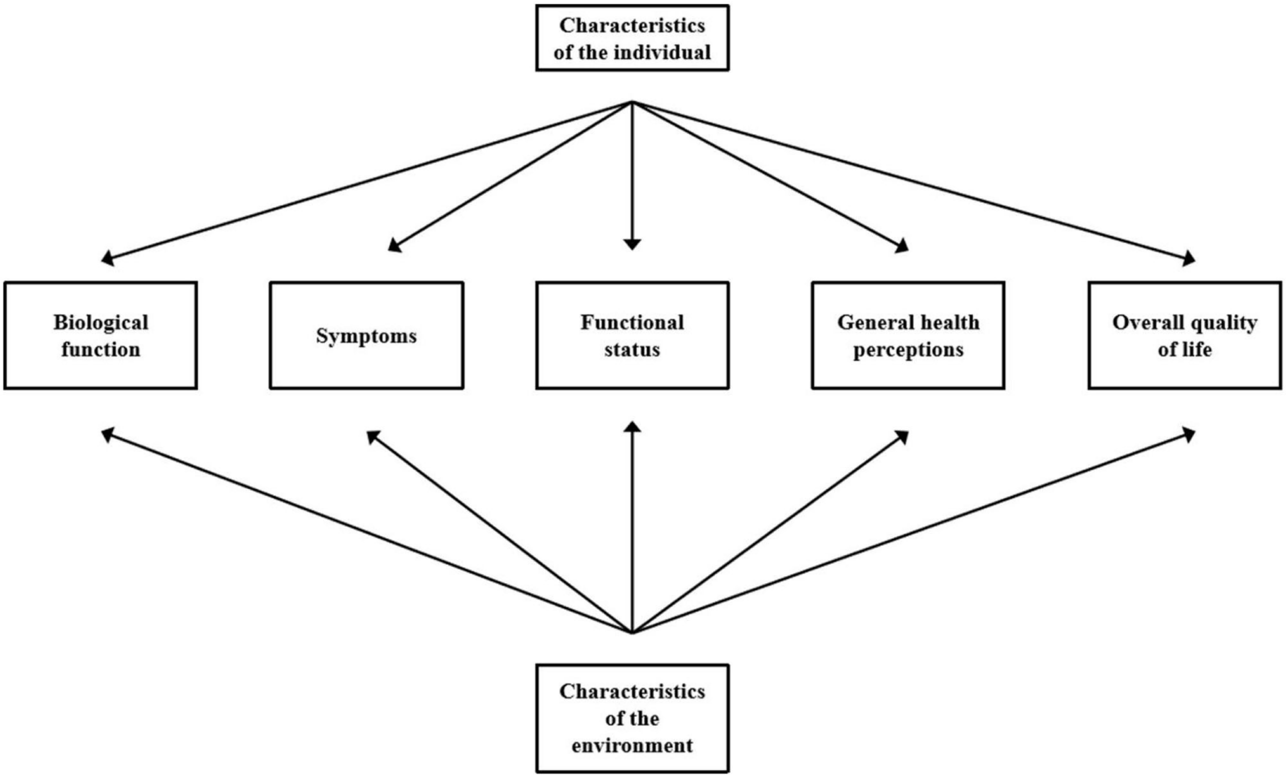

FIGURE 1 | Revised Wilson and Cleary model of health-related quality of life. Adapted from "Linking Clinical Variables with Health-Related Quality of Life: A Conceptual Model of Patient Outcomes," by Wilson and Cleary (26). Copyright by *JAMA*. Used with permission.

Altogether, 603 patients with RA were consecutively invited to participate in the cross-sectional study, and 580 (96.2%) were eventually included in the analysis. The Spearman correlation coefficient was used to determine the correlation between variables. The relationship between quality of life and other variables was evaluated by using the Structural Equation Model (SEM).

Data Collection and Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of Soochow University (SUDA20200225H11). All subjects meeting the criteria were asked to participate. Questionnaires were distributed by two well-trained researchers to the eligible participants. All participants were informed about (a) the aim and significance of this research, (b) confidentiality of patient data, and (c) that their engagement was totally voluntary, and they could withdraw from the research at any time. All data in the questionnaires that were completed were made confidential. A unique identification number was placed at the upper portion of the questionnaire.

Measurement Tools

The Body Image Disturbance Questionnaire comprised the following seven items (27): recognized concern, preoccupation, avoidance of role, the emotional suffering of their own appearance, as well as appearance impairment in social, educational, and work function. The Cronbach's alpha value was 0.877.

The patient's disease activity was measured using the Disease Activity Score in 28 joints (DAS28) (28). Four aspects were included in this questionnaire, which were calculated by using a software program that measures 28 swollen joint counts, 28 tender joint counts, the rate of erythrocyte sedimentation rate, as well as the patient's recognition of disease activity from 0 mm (not active at all) to 100 mm (very active).

Two sub-scales were included in the Hospital Anxiety and Depression Scale (HADS), which was used for measuring anxiety and depression over the prior month (29). Seven items could be found in each sub-scale. This evaluation tool has been used in large-scale studies. The Cronbach's alpha value of the questionnaire was 0.850, while the intraclass connection coefficient was 0.900.

The Fatigue Severity Scale questionnaire was used to assess fatigue severity (FSS) (30). It examined nine items; the average of all items served as the overall score, with the higher scores, indicating greater or severe fatigue. This tool has high reliability, high sensitivity, and internal consistency in fatigue evaluation. The Cronbach's alpha value of the questionnaire was 0.852.

The quality of sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI) (31). The Pittsburgh Sleep Quality Index consisted of 19 questions, which included seven aspects. Each aspect can have a score of 0 (no difficulty) to 3 (severe difficulty), with the total score ranging from 0 to 21. The Cronbach's alpha value of the questionnaire was 0.796.

The Short Form 36 Health Survey (SF-36) was used to assess QoL (32). It evaluated eight aspects. The scores ranged from 0 to 100, with higher scores indicating better health status. There were two forms of scores: the Z-transformed scores and the normalized domains scores. They were divided into physical components summary (PCS) and mental components summary (MCS) scores, with higher scores indicating better health status. The Chinese version of SF-36 has a Cronbach's alpha of 0.720 to 0.880.

The Global Pain Scale (GPS) includes 20 items related to participants' chronic pain experience (33). Participants indicated their responses on an 11-point scale (from 0 to 10). There were four subscales assessing pain, feelings, clinical outcomes, and activities. For the pain subscale, participants indicated the degree of pain felt currently along with their best, worst, and average pain during the last week, as well as whether they have felt less pain in the last week. The total Cronbach's alpha coefficient was 0.984.

Social Support Rating Scale (SSRS) (34), the Chinese version of SSRS, developed by Xiao Shuiyuan in 1994, was used to identify the social support status. SSRS, which consists of 10 items and three dimensions, was selected for its proven reliability and validity. The Cronbach's alpha of the total scale and subscales ranged from 0.825 to 0.896.

Statistical Analysis

SPSS version 25.0 (IBM, Armonk, NY, USA) was used for the statistical analysis. For measurement data, we first performed a normality test. If the data were normally distributed, measurement data were expressed by using means and standard deviations (SDs); if the data were not normally distributed, then the measurement data were expressed by the median and interquartile range; for categorical data, rates or composition ratios were used. R language (Vienna, Austria) was used to deal with missing values, using the Mice package (Multiple Imputation).

The SEM of SPSS version 25.0 (IBM, Armonk, NY, USA) was used for path analysis. The parameters of the model were estimated by the maximum likelihood method. First, the initial path model was adjusted based on two criteria. One was to delete insignificant paths, and the other was to use the modification index to establish the correlation between some residuals using the combination of professional knowledge to gain the best model.

RESULTS

A total of 603 patients with RA were consecutively invited to participate, and 580 (96.2%) were eventually included in the present study: 255 (44.0%) from Nantong, 120 (20.7%) from Henan, 101 (17.4%) from Suzhou, 55 (9.5%) from Changzhou, and 49 (8.4%) from Shanghai.

There were 603 questionnaires in total, of which 23 were considered invalid (e.g., with missing answers, highly similar

TABLE 1 | Characteristics of patients with RA ($n = 580$).

Variables	*N*/Mean/Median	%/SD/IQR
Gender		
Male	67	11.6%
Female	513	88.4%
Age (years)	51.04	24.65
BMI (kg/m^2)	22.36	4.07
Location		
City	132	22.8%
Town	162	27.9%
Suburb	286	49.3%
Marital status		
Married	529	91.2%
Unmarried	26	4.5%
Other	25	4.3%
Education		
≤9 years	80	13.8%
9–12 years	388	66.9%
>12 years	112	19.3%
Work status		
Employed	419	72.2%
Unemployed	81	14.0%
Student	5	0.9%
Other	75	12.9%
Yearly income (RMB)		
<15,000	184	31.7%
15,000–33,000	218	37.6%
>33,000	178	30.7%
Smoker		
Yes	69	11.9%
No	511	88.1%
Alcohol use		
Yes	90	15.5%
No	490	84.5%
Disease duration	4.0	(2.0, 9.0)
Hypertension		
Yes	85	14.7%
No	495	85.3%
Diabetes		
Yes	29	5%
No	551	95%
Coronary heart disease		
Yes	35	6%
No	545	94%
Nephropathy		
Yes	22	3.8%
No	558	96.2%
Other cardiopulmonary disease		
Yes	70	12.1%
No	510	87.9%
To be hospitalized		
Yes	206	35.6%
No	374	64.4%
Exercise frequency (/week)	0	(0.2)
Exercise duration (min)	0	(0.10)

IQR, interquartile range; RA, rheumatoid arthritis; RMB, renminbi; SD, standard deviation.

options). The response rate of the questionnaire was 96.2% (580/603) and the proportion of missing values for basic information was 0.7%, with missing information in area (1/580), age (2/580), and height (1/580); the proportion of missing values for other variables were as follows: BID 0.5% (3/580); social support 0.9% (5/580); sleep 1.0% (6/580); pain 0.5% (3/580); medication compliance 0.3% (2/580); and QoL 0.7% (4/580).

Characteristics of Patients

Table 1 shows the participants' baseline characteristics. The mean age of participants was 51.04 years (SD = 24.65), and 88.4% were female. Overall, 49.3% lived in a suburb. Most patients (91.2%) were married. Only 13.8% of the patients received education for ≤9 years. Most (72.2%) were employed, and 31.7% had yearly per capita incomes of <15,000 RMB. The mean disease duration was 4 years. Approximately 14.7% of patients had hypertension, 5% had diabetes, 6% had coronary heart disease, 3.8% had nephropathy, and 12.1% had another cardiopulmonary disease.

Total Scores of Scales

The mean (SD) of anxiety and depression scores were 10.67 (2.38) and 10.01 (2.39), respectively. The mean (SD) for each scale was 38.92 (7.35) for Fatigue Severity Scale, 26.00 (14.83) for BIDQ, 5.00 (1.50) for DAS28, 10.47(3.01) for PSQI, 55.91 (17.70) for Global Pain Scale, 177.26 (62.19) for PCS, 217.8 (64.63) for MCS, 436.57 (127.02) for the SF-36, and 37.48 (5.34) for SSRS.

Subgroup Differences

In **Table 2**, the PCS, MCS, and SF-36 total scores in our study were presented according to the sociodemographic and characteristics of the patients.

Correlations

The pain score had a significant correlation with DAS28, fatigue, sleep, and body image ($p < 0.01$). Body image score had a significant correlation with DAS28, depression, fatigue, sleep ($p < 0.01$). Sleep score had a significant correlation with depression, fatigue ($p < 0.01$).

Structural Equation Model

Figure 2 shows significant pathways in the final HRQoL model. We have successively removed the unimportant paths. Modification indices indicated no modifications. **Figure 2** shows the final model. The indices of the goodness-of-fit showed that the final model was an excellent fit to the data with root mean square error of approximation (RMSEA) of 0.072, goodness-of-fit index of 0.968, adjusted goodness of fit index of 0.928, normed fit index of 0.955, relative fit index of 0.916, incremental fit index of 0.936, and comparative fit index of 0.966. The direct, indirect, as well as the overall effects of predictors on HRQoL are demonstrated in **Figure 2**. Age and PF had an indirect effect on HRQoL. Among symptoms that had indirect effects on HRQoL through the physical function status, age exerted a direct influence on HRQoL and an indirect influence on HRQoL via PF. The direct effect value between QoL paths and the path correlation coefficient between symptoms are shown in **Figure 2**.

Fitting indicators of the model: ratio of chi square/df = 3.960; RMSEA = 0.072; goodness-of-fit index = 0.968; adjusted goodness of fit index = 0.928; normed fit index = 0.955; relative fit index = 0.916; incremental fit index = 0.966; Tacker-Lewis index = 0.936; and comparative fit index = 0.966. The coefficients of related factors were standardized, and the standardized regression coefficients were sorted. Symptoms and the standardized factor load of variables showed that the standardized load of pain was as high as 0.99, which is the most important factor affecting QoL. The standardized load of body image was 0.63, the standardized load of fatigue was 0.25, the standardized load of sleep quality was 0.24, the standardized load of depression was 0.07.

DISCUSSION

Wilson and Cleary's model-associated factors with global HRQoL environment variables were assessed in this study. This is the first large-sample multi-center cross-sectional survey using multiple variables to investigate the associations between the individual characteristics of patients with RA and overall HRQoL in China using SEM. The final model provided here shows an association between clinical variables, such as other underlying diseases, that mediate an individual's experience with actual symptoms, physical functioning, and general health on HRQoL. SEM allows the simultaneous assessment of the effects of personal and environmental characteristics on potential variables in the model. Our study and previous studies show that patients with RA often experience chronic pain and functional disabilities, including a high incidence of depression, body image disorders, fatigue, and sleep disorders with a decline in patients' QoL (35).

In the analysis of the subgroup, HRQoL scores were higher (indicating better QoL) in men than in women, the employed than in the unemployed, the college-educated individuals than in those with less educational levels, and in those in third-highest rank of income (¥15,000). The marital statuses were not associated with the HRQoL overall score, PCS, or MCS. These results are consistent with Gong's study findings and are worthy of attention (36). There were also significant differences in the QoL of patients with RA in different subgroups of age, disease duration, and comorbidities, which is consistent with Zeng's et al.'s study (35).

The presence of comorbidities may increase mortality in patients with RA. Further, treatment strategies may be affected, leading to worsening conditions. Fitting the SEM of the QoL of patients with RA in our study showed similar results for latent variables of biological factors, and both the number of comorbidities and risks, including coronary heart disease, diabetes, kidney disease, and fractures. Accordingly, the prediction and management of comorbidities are increasingly important in the long-term management of RA (37). What should not be ignored is that age as an individual characteristic not only had a constant effect on physical functioning but also on HRQoL. These data provide information about the prevalence, incidence, risk factors, and other characteristics of selected comorbidities, which may help identify comorbidities and management strategies.

TABLE 2 | Subgroup comparisons of 36-item short form survey physical component scores, mental component scores, and total scores.

Characteristic	PCS			MCS			SF-36		
	M	(SD)	*P*	*M*	(SD)	*P*	*M*	(SD)	*P*
Gender									
Male	167.39	45.11	0.074	200.73	39.88	0.001**	408.79	92.58	0.015*
Female	178.55	64		220.03	66.9		440.2	130.48	
Age (y)									
18–34	194.23	61.42	<0.001***	238.51	64.54	<0.001***	475.6	124.8	<0.001**
35–59	178.71	63.77		213.6	67.04		434.17	132.76	
≥60	153.02	51.43		201.5	52		393.56	99.84	
Location									
City	179.27	56.3	0.129	215.36	55.2	0.005**	440.28	110.4	0.028*
Town	184.38	63.63		231.59	70.9		456.47	136.33	
Suburb	172.29	63.7		211.12	63.95		423.53	127.55	
Marital status									
Married	191.69	64.45	0.305	231.36	57.71	0.508	464.4	121.81	0.453
Unmarried	176.03	62.89		216.93	66.06		434.64	129.52	
Other	188.2	39.66		222.22	32.46		448.42	59.98	
Education									
≤9 years	150.61	43.72	<0.001***	196.3	48.16	<0.001***	387.54	85.76	<0.001***
9–12 years	175.93	63.83		216.24	67.55		433.01	133.08	
>12 years	200.91	59.37		238.58	58.73		483.91	114.59	
Work status									
Employed	181.21	58.78	0.06	221.57	62.68	0.03*	443.3	122.57	0.15
Unemployed	162.67	76		198.49	70.89		408.99	144.66	
Student	190.8	72.7		232.17	75.55		442.97	136.77	
Other	170.04	61.83		216.64	65.14		428.35	128.73	
Yearly income (RMB)									
<15,000	164.55	68.92	<0.001***	209.36	75.61	0.02*	412.37	144.06	0.001**
15,000–33,000	177.06	56.24		216.51	56.69		434.62	114.75	
>33,000	190.63	59.27		228.11	60.25		463.97	117.51	
Smoker									
Yes	176.19	34.89	0.879	210.84	36.09	0.341	427.61	63.84	0.533
No	177.4	65.02		218.74	67.53		437.78	133.27	
Alcohol use									
Yes	180.13	49.57	0.634	214.17	51.48	0.562	435.14	97.79	0.907
No	176.73	64.26		218.8	66.79		436.83	131.76	
Disease duration									
≤1	175.02	68.23	<0.001***	220.65	78.39	0.62	428.42	143.92	0.017*
1–3	190.74	61.46		221.22	59.69		456.06	121.9	
3–5	189.18	53.11		220.08	54.75		455.13	109.35	
≥5	164.43	61.47		213.42	65.4		419.52	128.01	
Comorbidities									
No	180.21	65.23	0.122	223.09	70.56	0.008**	445.11	137.02	0.028*
Yes	171.85	55.94		208.12	50.82		420.95	104.84	
Exercise									
No	175.55	65.25	0.387	216.28	68.43	0.46	433.7	134.37	0.478
Yes	180.18	56.6		220.8	64.63		441.47	113.47	
BMI									
<18.5 kg/m^2	175.56	53.79	0.966	213.66	62.79	0.311	431.95	117.09	0.651
18.5–23.9 kg/m^2	177.7	59.92		220.77	62.52		440.09	121.77	
≥24 kg/m^2	176.75	70.73		211.67	70.38		429.17	143.4	

BMI, body mass index; MCS, mental component score; PCS, physical component score; RMB, renminbi; SF-36, The Short Form 36 health survey.
<0.05, **<0.01, and *<0.001.*

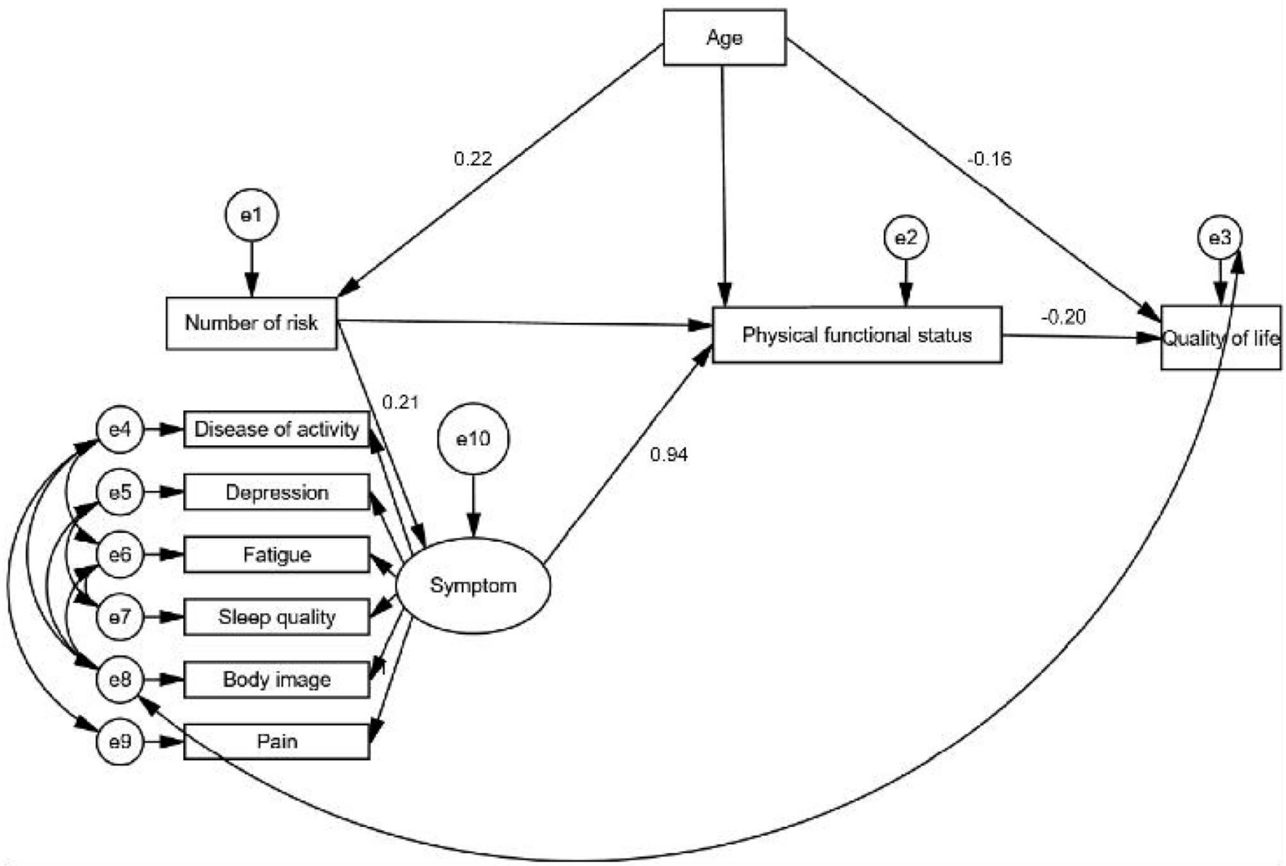

FIGURE 2 | Goodness of fit of structural equation models of variables in a cross-sectional study of health-related quality of life. (1) Latent variable: biological and physiological status; measured variables: number of risk factors (e.g., hyperlipidemia, diabetes). (2) Latent variable: symptom status; measured variable: BIDQ, DAS28, HADS, FSS, PSQI, and GPS. BIDQ, Body Image Disturbance Questionnaire; DAS28, Disease Activity Score in 28 joints; HADS, Hospital Anxiety and Depression Scale; FSS, Fatigue Severity Scale questionnaire; PSQI, Pittsburgh Sleep Quality Index; GPS, Global Pain Scale. (3) Latent variable: physical functional status; measured variable: physical function status was based on the total score of "go to the store," "do chores in my home," "enjoy my friends and family," "exercise," and "participate in my favorite hobbies" in GPS. GPS, Global Pain Scale. (4) Latent variable: QoL; measured variable: SF-36 total score. QoL, quality of life; SF-36, Short Form 36 Health Survey. (5) Latent variable: characteristics of the environment; measured variable: social support. (6) Latent variable: characteristics of the individual measured variable: demographic characteristics (age, education, income, etc).

Joint pain is often the first symptom. The definition of pain has been revised to "An unpleasant sensory and emotional experience associated with the diagnosis, treatment as well as rehabilitation of RA shows a long-term, dynamic together with complicated pragmatic procedure with, or resembling that associated with, actual or potential tissue damage" (38). In addition, there is an involvement of sensory perception, which is implicated in emotional processes and negative outcomes. Importantly, the unique sensory processing patterns of individuals have been reported as crucial factors in determining negative outcomes in the clinical practice and play a role in the prediction of their QoL (39). In our study, in order to fully evaluate the multidimensional and complex pain of RA patients, pain assessment was performed using Global Pain Scale; this is the first time that a comprehensive pain assessment was applied to RA patients. It is also an innovative approach used in this study. In the SEM results, a better fit may also better reflect the patient's complications, in terms of pain, feelings, outcomes, and activities. Chronic disease, such as RA, is characterized by its uncertain course, and its frequent confrontation with pain and fatigue, and the possibility of becoming disabled influence the patients' psychological well-being. Notably, the results of our Pearson's correlation analysis showed that pain correlates with disease activity, fatigue, sleep quality, and physical image disorders, and in the results of the SEM, the standardized load of pain is up to 0.99, which is sufficient to prove that pain plays a decisive role in QoL. This suggests that we should pay attention to the pain symptoms and related symptom groups, strengthen the symptom management of RA patients, and improve the QoL of RA patients.

Disease activity was assessed by using the DAS28. Our results showed that the DAS28 score was 5.00 (1.50), which was more severe than the results of previous research (40), SEM shows that disease activity interacts with fatigue, BID, and pain, and affects body function. These results are completely consistent with the results of the Pearson's correlation analysis.

In patients with RA, fatigue is considered the most common extra-articular symptom other than pain. Among patients with RA. Our study found that 64.8% of patients considered fatigue the most important issue. In the correlation analysis, fatigue was associated with pain, BID, and sleep quality. In SEM, it was also shown to interact with increased disease activity, with a standardized load factor of 0.25, ranking fourth among the symptom groups. This is similar to the findings of Gong's study (36). Pain is the dominant factor in the experience and degree of fatigue. Disease activity is positively correlated to fatigue. Thus, fatigue has been shown to cause notable adverse consequences and to affect every aspect of daily life, bringing a considerable human and economic burden to QoL, thereby reducing the overall health of patients (41).

Psychological well-being refers to an individual's mood in a global sense. When someone is confronted with uncertainty, threat, and ambiguity, this may provoke feelings of depression. Our results show that 76.4% of patients with RA experienced depression. Patients with RA and depression had significantly lower medication compliance, impaired physical function, sleep quality, and QoL than those without depression (42). Sleep disturbances can be often observed in patients who have long-term diseases; meanwhile, the prevalence of poor sleep is higher in patients with RA than in those without RA.

Body image (BI) is defined as "the attitudes and perceptions of individuals toward their appearance and their beliefs and others with respect to their body." It is strongly influenced by one's health and may be associated with abnormal coping behavior, psychopathology, poor outcomes, and HRQoL (43). As RA progresses, some patients may have irreversible damage, such as joint deformities, reduced restrictions on movement, and function, which may lead to psychological problems, such as human BID (44). Our results showed that almost all patients observe their BI and have different degrees of BID. In the correlation analysis, BID was associated with disease activity, fatigue, depression, sleep quality, pain, and, interestingly, SEM. In addition to indirect effects on QoL, BI directly affects the QoL. The standard factor load is 0.63, which plays a decisive role in pain. It is likely to be a mediating effect in the RA QoL model. The important conclusion of the study is also the innovation of this study, which deserves more attention from rheumatologists.

The QoL of patients with RA is a complex systemic response, which is determined by the patient's biological characteristics. There are different multivariable symptom group interactions, and it is not possible to simply explore the correlations of several variables. A systematic study is needed, and important factors should be assessed by using multi-factor analysis and SEM to verify its causality. In our research hypothesis, social support played a role in the QoL model as an environmental feature but it was included in the final model verification, differing from the results of another study on the QoL of patients with RA (45). It may be that their research is more related to the factorial analysis of its relevance to the social quality, but it is similar to Gong's results (36). Social support is a long-term process, associated with factors, such as the route and frequency of social support, and patient demand. This suggests that we should conduct a comprehensive and dynamic evaluation of the entire process in the patient support system, as needed while paying attention to the selected methods and durations to improve the QoL of patients with RA.

There are some limitations to this study. First, self-reporting was used to assess the patient's condition. It is difficult to avoid recall and reporting biases, which may have affected the association between variables. Second, this was a multi-center cross-sectional survey. Future research should focus longitudinally on the QoL of patients with RA and explore intermediary factors affecting their QoL, Qualitative research will be combined with patient interviews to focus on the vertical regularity of the deterioration of QoL, the needs, cognition, and experience in the course of the disease. We should also pay attention to the influence of environmental factors, coping style, and symptom management on patients' quality of life to provide better evidence to establish effective interventions.

In conclusion, this study analyzed the QoL of patients with RA in China through a multi-center survey. The QoL model was used to fit an SEM to systematically verify and analyze the population disease data, biological factors, and the direct and indirect effects of the symptom group on the QoL, and the interactions between the symptoms. Our results showed that age and comorbidities would directly influence QoL, pain, BI, disease activity, fatigue, sleep quality as and depression, which are ranked according to whether the effects are important to the patient's physical function and on the patient's QoL. BI has a direct impact on QoL. Therefore, the RA diagnosis and treatment and rehabilitation of RA patients is a long-term, dynamic and complex practical process. Patients' personal symptoms, needs, and experiences also vary greatly. Comprehensive assessment of patients' symptoms, needs, and experiences, at the same time, the role of social support cannot be ignored, as they can help to meet patients' nursing needs, improve their mood and pain-based symptom management, and ultimately improve patients' QoL.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of Soochow University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BS and HC performed the experiment, analyzed the data, and prepared the figures and the manuscript. BS, HC, AD, RX, YG, and XC collected the data. DY analyzed the data. G-YX, HL, OY, and CY designed, supervised the experiments, and finalized the manuscript. All the authors have read and approved the manuscript.

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Resilience as a Mediator of the Association Between Perceived Stigma and Quality of Life Among People With Inflammatory Bowel Disease

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Background: Improving Quality of Life (QOL) is an essential objective in the management of inflammatory bowel disease. An accumulating body of research has been conducted to explore the association between perceived stigma and QOL among patients with chronic illness. Still, underlying mechanisms behind this pathway have not been thoroughly examined.

Objective: To investigate (a) the effect of perceived stigma on QOL among patients with inflammatory bowel disease; and (b) the mediating role of resilience in the association between perceived stigma and QOL.

Methods: This cross-sectional study included a convenient sample of patients diagnosed with inflammatory bowel disease from four tertiary hospitals in Jiangsu Province, China. Patients completed the Perceived Stigma Scale in Inflammatory Bowel Disease (PSS-IBD), the Resilience Scale for Patients with Inflammatory Bowel Disease (RS-IBD), and the Inflammatory Bowel Disease Questionnaire (IBDQ). A bootstrapping analysis was implemented using the SPSS macro PROCESS.

Results: A total of 311 patients with Cohn's disease and ulcerative colitis participated in this study, and 57.6% were men. The mean disease duration was 3.51 ± 1.04 years. Approximately 40% of the sample exceeded the criterion score for moderate stigma. Patients who perceived moderate or severe stigma reported lower QOL compared with those with mild stigma. After controlling for sociodemographic and clinical variables, we observed that perceived stigma was negatively associated with resilience. Moreover, resilience was found to mediate the relationship between perceived stigma and all aspects of QOL.

Conclusions: These findings suggested that QOL of patients with inflammatory bowel disease was associated with perceived stigma and resilience and identified the mediating effects of resilience in the relationship between perceived stigma and QOL. Furthermore, this suggests that integrating intervention techniques to target resilience into the QOL improvement program of individuals with perceived stigma is possible.

Keywords: resilience, perceived stigma, quality of life, mediating effect, inflammatory bowel disease

INTRODUCTION

Inflammatory bowel disease (IBD), mainly comprising Cohn's disease (CD) and ulcerative colitis (UC), are immune-mediated intestinal inflammatory disorders characterized by early-onset. Recently epidemiological data show that approximately 6.9 million individuals worldwide are living with IBD (1). Moreover, the incidence and prevalence of IBD are still increasing, especially in newly industrialized countries. Patients with IBD suffer from abdominal pain, diarrhea, rectal bleeding, and frequent bowel movements throughout their lifetime repeatedly (2, 3). Treatment for IBD largely depends on pharmacological means, but surgery is often needed when complications occur (4). It is estimated that the overall 10-year risk of surgery after diagnosis is 39.5% for CD and 13.3% for UC (5).

The quality of life (QOL) among patients with IBD is of growing significance since the patient-reported outcomes are recognized as primary endpoints by regulatory agencies (6). QOL is a broad multidimensional concept that involves objective and subjective aspects, focusing on the physical, emotional, mental, and social impact of the disease on patients' lives (7). Traumatic childhood experiences, sensory processing patterns, and chronic disease are recognized risk factors for QOL (8, 9). As an uncommon, chronic disease, IBD seriously impairs the QOL of patients (10–12). A recent meta-analysis performed by Knowles and his colleagues indicated that QOL was significantly lower for those with IBD relative to healthy controls (13). QOL among patients with IBD may be influenced by disease symptoms, treatment regimen, and various psychosocial variables (14). Psychosocial variables could affect the patients' psychological and social functions and alter gastrointestinal physiology by activating the microbiota-brain-gut axis, leading to decreased or improved QOL (15–18). Sweeney and her colleagues reported that depression, fear avoidance, and catastrophizing were risk factors for IBD -related pain, while self-efficacy and mental well-being were protective factors (19). Recently, the perceived stigma has been considered a prominent psychosocial variable that damage QOL (20). Therefore, the understanding of QOL should pay attention to the physical distress caused by IBD and consider perceived stigma and other psychosocial factors.

Perceived stigma is defined as individuals' feelings that other persons hold negative attitudes or negative beliefs about them and their condition (21). Risks of incontinence in public, the changes in body image, negative impacts on sexual life, and burdens to others make patients with IBD susceptible to perceived stigma (22). Taft TH et al. investigated the prevalence of stigma in patients with IBD and reported that 84% of participants had perceived stigma (23). Literature outside the field of IBD has demonstrated that higher levels of perceived stigma are associated with poorer QOL (24–26). While perceived stigma is identified as a specific concern for patients with IBD, only one study to date has proved the negative relationship between perceived stigma and QOL (23).

Moreover, the specific mechanisms by which perceived stigma affects QOL in patients with IBD remain elucidated. As not all IBD patients who perceive stigma have poor QOL, it is plausible to assume that some factors may mediate such a connection (27, 28). Resilience, one of the most mentioned positive psychological resources, is usually defined from three perspectives in chronic disease: traits, outcome, and process. For example, (1) traits reflecting the characteristics of tenacity and flexibility in response to disease-related stress; (2) positive health outcomes in high-risk patients; (3) a dynamic process of successful adaptation when exposed to chronic disease (29). There is a debate concerning how to define resilience, but previous research has identified the role of 'resiliency training programs,' which infers it is modifiable (29). In our study, resilience is a quantifiable and modifiable personal quality that enables individuals to bounce back from IBD-related adversity (30). Resilient patients could cope with their disease adaptively. Neurological evidence revealed that resilience could invoke specific brain structures and neural circuits to help the individual to regulate emotion and adopt adaptive social behavior (17, 18). Resilience was reported to positively predict QOL in adolescents with type 1 diabetes and patients with acute myocardial infarction (31). Among people living with IBD, higher levels of resilience were significantly associated with better QOL (32, 33). Perceived stigma from family members, spouse, friends, employers, and colleagues affects resilience. A qualitative study revealed that stigma is more pronounced in less resilient IBD patients, especially in those lacking support networks (34). Self-esteem, mastery, and optimism, which are essential components of resilience, could be reduced by perceived stigma (35). Hsiung et al. found that mastery mediates the association between perceived stigma and QOL in patients with schizophrenia (36). The above evidence suggested that perceived stigma might impair resilience by causing low self-esteem, mastery, and pessimism, sequentially affecting QOL. However, no studies have analyzed the relationship between perceived stigma, resilience, and QOL among patients with IBD to our knowledge.

The present study aims to explore the impact of perceived stigma on QOL and investigate the mediating effects of resilience in the path from perceived stigma to QOL among patients with IBD. First, we hypothesized that perceived stigma was negatively associated with QOL among patients with IBD. Second, we further supposed that resilience could mediate the link between perceived stigma and QOL in these patients.

MATERIALS AND METHODS

Participants and Procedure

Patients with IBD were recruited from the Digestive Department of four tertiary hospitals in Jiangsu Province, China, using consecutive sampling. Participants were referred by their charge nurse if they were (1) diagnosed with UC or CD according to the current diagnostic criteria (2, 3); age≥18 years; (3) disease duration of more than 6 months; (4) education level of all participants was elementary school or above, able to read and understand the questionnaire. Exclusion criteria included: (1) severe mental illness (such as schizophrenia, bipolar disorder, paranoiac psychosis); (2) malignant tumors or other chronic diseases (such as heart failure, diabetes); (3) combined with other intestines or anorectal disease. The first authors introduced the purpose, procedures, and potential benefits and risks of the study. All the patients were asked to give written informed consent if they were eligible for the study. Next, the patients completed a set of self-reported questionnaires in a quiet room at each clinical site, including demographic (age, gender, education level, marital status, residence, family income) and clinical (disease type, duration) information. Modified Truelove and Witts' Severity Index and Harvey Bradshaw Simple Index were used to measure the disease activity of UC and CD patients, respectively, by their nurse in charge. We used G.Power 3.1 to calculate the sample size. The results showed that the data from 257 patients with UC and CD would give sufficient power (0.90) to detect a small effect size (0.05) on quality of life, explained by 13 independent variables (the perceived stigma, resilience, demographic, and clinical variables), with alpha = 0.05.

Of the 343 patients who were interested in participating and screened for eligibility, 320 were eligible. Three hundred twenty patients signed the informed consent and finished the questionnaires. Because of the incompletely filled questionnaires, nine respondents were excluded from the study. Finally, the data of 311 participants were used for the data analysis. **Figure 1** showed the participant recruitment process in detail.

Instruments

Perceived Stigma

The Perceived Stigma Scale in IBD (PSS-IBD) is a 10-item instrument designed to determine the presence of perceived stigma (23). Items are rated on a five-point scale ranging from 0 (Never) to 4 (always) and evaluated for six social domains. A total score of perceived stigma can be obtained by summing the scores of all six social dimensions. Scores of 1–80 indicate low stigma, 81–160 represent moderate stigma, and scores equal to or above 161 suggest high stigma. The PSS-IBD has been proved to have adequate reliability in American and Chinese patients with IBD (Cronbach's alpha = 0.89 and 0.96, respectively) (23, 37).

Resilience

The Resilience Scale for Patients with Inflammatory Bowel Disease (RS-IBD) is a specific resilience instrument for patients with IBD developed in China (38). The RS-IBD includes 25 items that are classified into six dimensions. Each item is scored on a five-point scale ranging from 1 (not true at all) to 5 (true all the time), with higher scores suggesting higher resilience. The RS-IBD was reported to have adequate reliability and construct validity in Chinese people with IBD (38).

Quality of Life

Quality of life was assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ), a 32 items instrument developed in Canada (39). The IBDQ comprises four dimensions: bowel symptoms, systemic symptoms, emotional function, and social function. The IBDQ rated on a seven-point Likert scale, ranging from 1 to 7. The scale's total score can be calculated by summing the scores of all dimensions, with higher scores indicating better QOL. The Chinese version of the IBDQ was reported to exhibit adequate internal consistency reliability (Cronbach's alpha, 0.95), split-half reliability (0.90), and construct validity (four factors accounted for 60.99% of the variation) (40).

Disease Activity

For UC, the disease activity was assessed by modified Truelove and Witts' Severity Index (41, 42). Truelove and Witts' Severity Index involves the number of bloody stools per day, body temperature, pulse, hemoglobin, and erythrocyte sedimentation rate. Patients with UC stratified as having four scores or less were regarded as being in remission, while those with four or more were in the active stage. We adopted the Harvey Bradshaw Simple Index to assess the disease activity of CD. This scale is widely used in clinical practice and scientific research (41, 43). It comprises five aspects: overall well-being, the severity of abdominal pain, the daily number of liquid stools, abdominal lumps, and complications. Patients with CD categorized as having four scores or less were regarded as being in remission, while those with four or more were considered with active disease.

Statistical Analyses

Statistical analyses were performed using IBM SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA). In this cross-sectional study, descriptive statistics were computed for all study variables. Before the analysis, the Kolmogorov-Smirnov test was used to determine whether the numeric variables showed a normal distribution. Next, the *t*-test and analysis of variance (ANOVA) were applied to compare the QOL among patients with different sociodemographic and clinical characteristics. The relationships between perceived stigma, resilience, and QOL were assessed utilizing Pearson's bivariate Correlation. Finally, we performed a bias-corrected bootstrapping analysis (with 5000 resamples) using the SPSS macro–PROCESS Model 4 to verify the mediating effects of resilience. The mediating effect was considered statistically significant if the 95% bootstrap confidence interval did not contain zero (44). Sub-group analysis was performed based on disease activity (remission vs. active

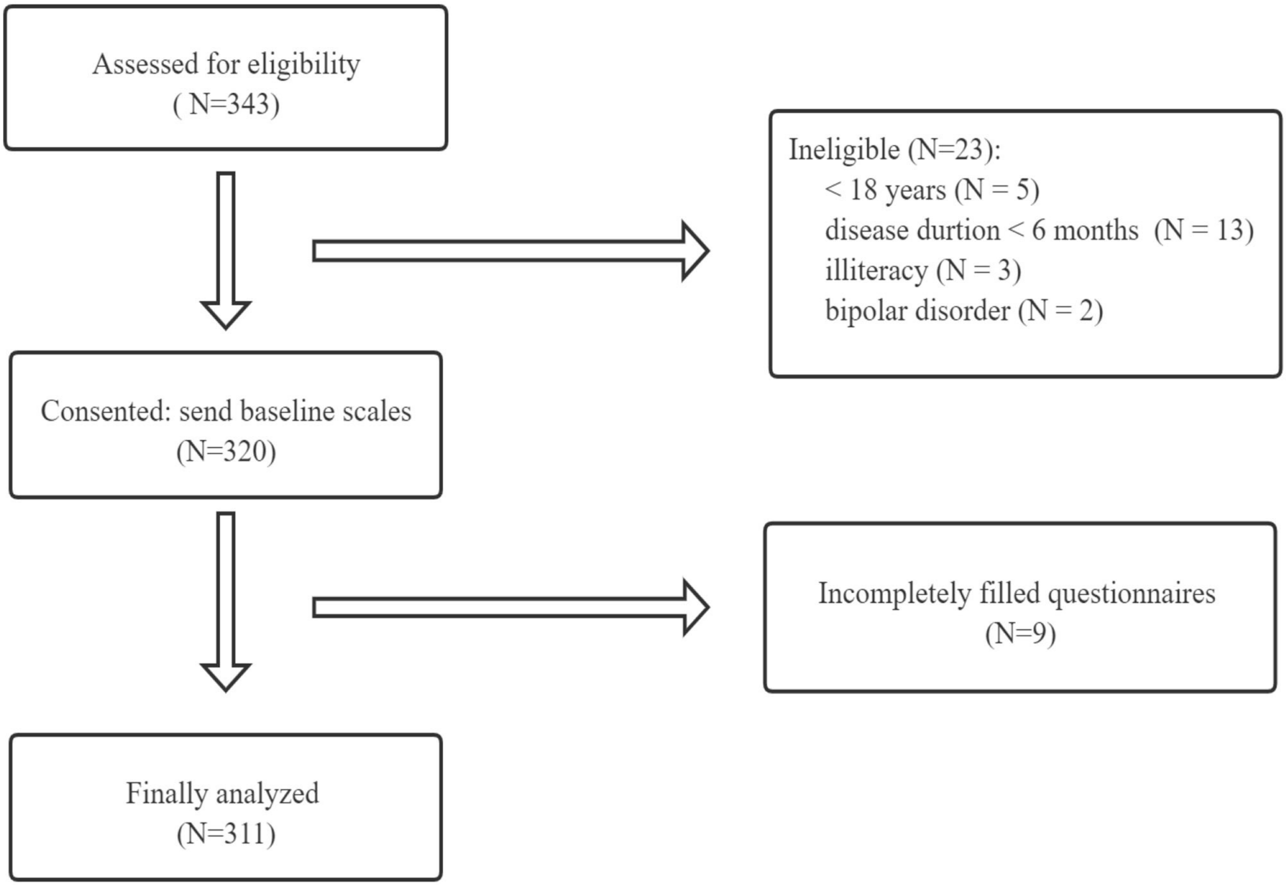

FIGURE 1 | Participant recruitment flow chart.

disease). The interactions of disease activity and perceived stigma and resilience were also explored. All statistical tests were performed at a 0.05 level of significance.

RESULTS

Participants' Sociodemographic and Clinical Characteristics

The final sample consisted of 311 patients with IBD. Their mean age was 33.70 ± 11.62 (mean ± standard deviation) years, and 57.6% were men. Nearly half of the participants (42.7%) had a higher education level, and 224 participants (72.0%) lived in the cities. Seventy-nine patients (25.4%) were divorced, and 149 patients (47.9%) were married. More than half of the sample (60.1%) had an annual household income of 50,000 Yuan or more. On disease type, 69.5% of patients were diagnosed with CD. The mean duration time since diagnosis was 3.51 ± 1.04 years. Most of them (67.2%) were in remission (**Table 1**).

Quality of life did not differ significantly among patients of different ages, gender, education level, or disease duration groups. However, there were differences related to marital status, residence, income, disease type, and disease activity (all $P < 0.05$). The details of participants' characteristics and differences in quality of life were summarized in **Table 1**.

Descriptive Characteristics of Target Variables and Relationships Among Them

The mean score for perceived stigma was 71.60 ± 18.73, with 38.9% of the participants having scores above the criterion score of 80 for moderate stigma. The mean score for resilience was 95.63 ± 15.57 of 125. In terms of QOL, the mean score was 139.01 ± 21.13. The subscale of bowel symptoms had the highest mean score of the items (5.50), followed by emotional function (5.20), social function (5.16), and systemic symptoms (4.87).

Table 2 presents the results of bivariate analyses. Significant correlation was found between perceived stigma and resilience ($r = -0.326$, $P < 0.01$). All subscales of QOL were found to be negatively associated with perceived stigma but positively correlated with resilience. Moreover, patients who reported moderate or severe stigma had significantly lower scores in QOL compared with those who reported mild stigma (See detail in **Table 3**).

TABLE 1 | Demographic and clinical characteristic differences in scores of quality of life.

Characteristics	*N* (%)	Quality of life mean (±SD)
Gender		
Male	179 (57.6)	160.66 ± 32.94
Female	132 (42.4)	165.69 ± 34.49
p-value		0.348
Education level		
Primary education	63 (20.3)	164.90 ± 32.46
Secondary education	115 (37.0)	166.20 ± 35.16
Higher education	133 (42.7)	172.30 ± 32.05
p-value		0.223
Marital status		
Unmarried	83 (26.7)	177.83 ± 31.68
Married	149 (47.9)	172.49 ± 30.81
Divorced	79 (25.4)	151.35 ± 33.89
p-value		0.000
Residence		
City	224 (72.0)	171.27 ± 30.85
Country	87 (28.0)	161.53 ± 38.43
p-value		0.021
Family yearly income, Yuan		
<50,000	124 (39.9)	162.92 ± 34.99
≥50, 000	187 (60.1)	172.28 ± 31.80
p-value		0.015
Disease type		
Crohn	216 (69.5)	173.17 ± 31.78
Ulcerative colitis	95 (30.5)	158.03 ± 34.66
p-value		0.000
Disease duration, years		
<2	125 (40.2)	170.24 ± 32.58
2–5	125 (40.2)	165.66 ± 34.34
>5	61 (19.6)	170.98 ± 33.07
p-value		0.455
Disease activity		
Remission	209 (67.2)	178.69 ± 23.31
Active stage	102 (32.8)	147.75 ± 36.65
p-value		0.000

The Mediating Effect of Resilience on the Association Between Perceived Stigma and Quality of Life

We used "Model 4" in the PROCESS macro to test the mediating effect of resilience on the association between perceived stigma and QOL. Quality of life varied significantly depending on marital status, residence, income, disease type, and disease activity (**Table 1**). Therefore, those five variables were dummy coded and assigned as covariates in the test.

As seen in **Table 4**, the total effect of perceived stigma on all aspects of QOL were significant [bowel symptoms ($\beta = -0.052$, $SE = 0.014$, $P = 0.000$), systemic symptoms ($\beta = -0.025$, $SE = 0.008$, $P = 0.002$), emotional function ($\beta = -0.109$, $SE = 0.016$, $P = 0.000$), and social function ($\beta = -0.052$, $SE = 0.010$, $P = 0.000$)].

Figure 2 shows the mediation model. The paths from perceived stigma through resilience to all aspects of QOL were significant. These included the products of the path from perceived stigma to resilience ($P = 0.000$) and the path from resilience to bowel symptoms ($P = 0.000$), systemic symptoms ($P = 0.000$), emotional function ($P = 0.001$) and social function ($P = 0.000$). Although perceived stigma had no direct effects on bowel symptoms and systemic symptoms, it directly affected emotional function and social function.

The result from bias-corrected bootstrapping indicated a significant indirect effect from perceived stigma to resilience to all aspects of QOL [bowel symptoms ($\beta = -0.026$, $SE_{Boot} = 0.007$, 95%CI: -0.041, -0.014), systemic symptoms ($\beta = -0.014$, $SE_{Boot} = 0.004$, 95%CI: -0.023, -0.007), emotional function ($\beta = -0.033$, $SE_{Boot} = 0.009$, 95%CI: -0.053, -0.018), and social function ($\beta = -0.016$, $SE_{Boot} = 0.005$, 95% CI: -0.026,-0.008)]. Therefore, resilience was found to mediate the relationship between perceived stigma and QOL.

In subgroup analysis stratified by disease activity, the perceived stigma was significantly negatively associated with QOL in both remission group ($\beta = -0.304$, $t = -4.598$, $P = 0.000$) and active disease group ($\beta = -0.288$, $t = -3.005$, $P = 0.003$), $P_{perceivedstigma-interaction} = 0.425$. Moreover, the resilience was significantly positively associated with QOL in both remission group ($\beta = 0.401$, $t = 6.295$, $P = 0.000$) and active disease group ($\beta = 0.210$, $t = 3.811$, $P = 0.000$), $P_{resilience-interaction} = 0.639$.

DISCUSSION

The main finding of the present study was that resilience could mediate the effect of perceived stigma on QOL in patients with IBD after statistically controlling for marital status, residence, income, disease type, and disease activity. In other words, perceived stigma might impair an individual's resilience and subsequently influenced QOL. Therefore, perceived stigma and resilience should be considered significant psychosocial variables in promoting QOL among patients with IBD.

This study revealed that the perceived stigma directly affected the emotional function and social function dimensions of QOL. Consistent with this finding, Gamwell et al. observed that more significant perceived stigma directly aggravated depressive symptoms and weakened the bonds between youth with IBD and society (45). Patients with IBD tend to perceive illness-related stigma because of public misconceptions about etiology, variability in course, and fear of incontinence, which leads to concealment and social withdrawal (22, 46). The concealment of disease could probably decrease communication and connections with others, increasing feelings of isolation and depression (47). However, since not all patients perceived stigma had a poor QOL, some authors pointed out that additional factors should be considered when explaining how psychosocial burden exerts adverse effects. Similar to earlier conclusions, we illustrated that resilience played a mediating role in the associations

TABLE 2 | Levels and association of patients' quality of life with perceived stigma and resilience ($N = 311$).

			Correlation matrix						
	Mean	**SD**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1. Perceived stigma	71.60	18.73	1						
2. Resilience	95.63	15.57	−0.326**	1					
3. Quality of life	139.01	21.13	−0.290**	0.392**	1				
4. Bowel symptoms	56.03	10.92	−0.198**	0.345**	0.917**	1			
5. Systemic symptoms	24.36	6.02	−0.173**	0.302**	0.876**	0.775**	1		
6. Emotional function	62.34	12.22	−0.354**	0.409**	0.938**	0.780**	0.773**	1	
7. Social function	25.82	7.51	−0.287**	0.330**	0.882**	0.733**	0.708**	0.790**	1

***Correlation is significant at the 0.01 level (2-tailed).*

TABLE 3 | Comparison of quality of life between the patients with mild, moderate and severe perceived stigma ($N = 311$).

Subscales of QOL	**Mild stigma^a($N = 190$)**	**Moderate stigma^b ($N = 115$)**	**Severe stigma^c ($N = 6$)**	***P***
Bowel symptoms	57.54 ± 10.35	53.82 ± 11.56	50.50 ± 7.45	0.007 a > b
Systemic symptoms	25.13 ± 6.00	23.26 ± 5.90	21.17 ± 4.88	0.013 a > b
Emotional function	65.48 ± 11.30	57.99 ± 11.95	46.00 ± 6.60	0.000 a > b,c
Social function	27.48 ± 7.04	23.49 ± 7.50	18.00 ± 6.07	0.000 a > b,c
Total score	175.63 ± 31.44	158.56 ± 33.66	135.67 ± 18.27	0.000 a > b,c

^{a,b,c}*Scheffé test.*

between perceived stigma and emotional and social function (48, 49). Resilience could help individuals adopt positive coping strategies (disclosure and seeking support) to maintain good psychosocial function (34). Higher levels of resilience are reportedly associated with fewer negative emotions and better interpersonal communication (15, 16, 50). In terms of neuro mechanisms, resilience could invoke specific brain structures and neural circuits, prompting the individual to regulate emotion and engage in prosocial behavior (17, 18).

Although we failed to find direct associations between perceived stigma and bowel symptoms and systematic symptoms dimensions of QOL, perceived stigma affected the bowel and systematic symptoms by reducing resilience. Resilience is a positive predictor of self-management in patients with chronic diseases (51, 52). Resilient patients are prone to adopt more self-management behaviors to achieve disease control (53, 54). Mediating effects between psychosocial burden and physical outcomes have been shown for various positive personality traits. Cherrington et al. reported that self-efficacy played an intermediary role in the path from depression to glycemic control in male diabetic patients (55). In a cross-sectional study conducted in patients with colorectal cancer, the variance anxiety accounted for preoperative insomnia increased after adding self-esteem to the hierarchical regression model (56). Resilience as a mediator of the association between perceived stigma and bowel and systematic symptoms has never been reported. Still, it is plausible considering that self-efficacy and self-esteem are integral parts of resilience (54). In other aspects, earlier studies demonstrated that perceived stigma was a prominent risk factor of depression and anxiety, especially for people with low resilience (49, 57, 58). The physiological mechanism of microbiota-brain-gut axis regulation could clarify how psychosocial burden can aggravate bowel and systematic symptoms in patients with IBD (59). The microbiota-brain-gut axis involved the central systems, autonomic nervous systems, endocrine system, immune system, and intestinal microenvironment. Stress responses caused by psychological disorders might activate the microbiota-brain-gut axis and further bring about altered gastrointestinal physiology, resulting in bowel and systematic symptoms (59, 60). These previous studies supported our current findings that resilience played a mediating role between perceived stigma and somatic symptoms.

Several limitations should be noted in the present study. Firstly, our study adopted a cross-sectional design, which could not confirm the causal associations between study variables. The effects of perceived stigma and resilience on QOL should be investigated and verified in more prospective studies to provide more reliable evidence. Secondly, the findings of this study should be generalized with caution because the sample in this study was mainly based on no-random participation. Random

TABLE 4 | Direct and indirect (mediation) effects of perceived stigma on quality of life ($N = 311$).

Independent variable	Effects	Bowel symptoms			Systemic symptoms			Emotional function			Social function		
		Estimate	SE	*P*	Estimate	SE	*P*	Estimate	SE	*P*	Estimate	SE	*P*
Perceived stigma	Total effect	−0.052	0.014	0.000	−0.025	0.008	0.002	−0.109	0.016	0.000	−0.052	0.010	0.000
	Direct effect	−0.026	0.014	0.063	−0.011	0.008	0.161	−0.076	0.016	0.000	−0.037	0.010	0.000
	Indirect effect through resilience*	−0.026	0.007	-	−0.014	0.004	-	−0.033	0.009	-	−0.016	0.005	-

**The results from bias-corrected bootstrapping.*

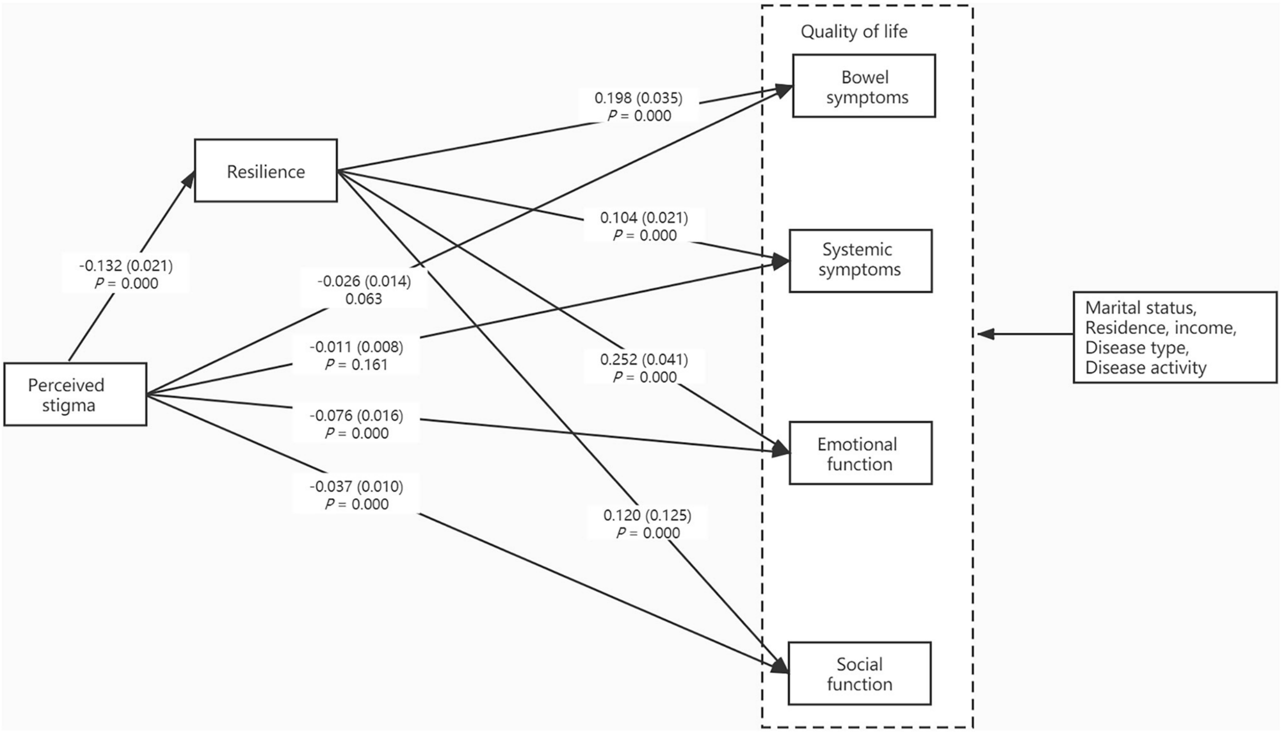

FIGURE 2 | The mediation model of perceived stigma, resilience, quality of life.

sampling could be considered in future research to confirm the findings of this study. Thirdly, except for the questionnaires measuring disease activity index, most questionnaires used in this survey, including PSS-IBD, RS-IBD, and IBDQ, came from the patients' self-reports which have subjectivities and thus easy to cause measure bias. In addition, we only included 95 patients with UC, which was insufficient to perform a subgroup analysis to determine the stability of the model in different disease types. Furthermore, the potential psychosocial mediating variables (such as self-esteem, mastery, and optimism), which are essential components of resilience, have not been analyzed. Last but not least, although CD and UC account for approximately 90% of IBD cases, there exist some patients with indeterminate colitis (1). This study only recruited patients with UC and CD. Despite the above limitations, the results presented here have significant implications. We tested the hypothesis that perceived stigma negatively affected QOL in patients with IBD and indirectly predicted QOL through resilience. The contribution of this study is to demonstrate the mediating effect of resilience on perceived stigma and QOL, which can add to the previous literature a potential mechanism whereby perceived stigma affects QOL. These findings implied that integrating intervention techniques to target resilience into the QOL improvement program of individuals with perceived stigma is feasible. There exist some resilience-enhancing programs for patients with chronic disease, such as the Be Resilient to Breast Cancer (BRBC) and Mindfulness-Based Stress Reduction (MBSR) (61, 62). Cognitive reframing is regarded as the active ingredient of resilience interventions (29). Lillis and his colleague adopted positive cognitive reframing strategies to interfere with obesity-related stigma (63). They found that the intervention group compared to the control group showed more significant mitigation of obesity-related stigma and improvement in QQL. Moreover, Kumpfer KL et al. suggested that the environmental resources (such as family and peer support) can promote resilience to help individuals positively cope with stressful events (64). A peer-led group program performed in adolescents with mental illness displayed a significant effect post-intervention, including reduced stigma stress and increased QOL (65). Therefore, resilience-oriented interventions that deliver disease knowledge and train interpersonal skills can be given to family members, peers, and coworkers of patients with IBD to increase social support and reduce perceived stigma (22, 66). As applied to clinical care, we recommend that healthcare providers incorporate perceived stigma and resilience assessment in patients' psychological screening and include cognitive reframing and support promotion in QOL improvement programs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of the First Affiliated Hospital of Nanjing Medical University approved all study procedures (no. 2019-SRFA-122). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DL and MZ designed the study, enrolled participants, analyzed and interpreted the data, and wrote the manuscript. LS, QB, ML, and SR were responsible for collecting data. ZL supervised this research project. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Effectiveness of Resilience Interventions on Psychosocial Outcomes for Persons With Neurocognitive Disorders: A Systematic Review and Meta-Analysis

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Background: Neurocognitive disorders, such as mild cognitive impairment (MCI), dementia, and Alzheimer's disease, not only harm people's cognitive function but also lead to negative emotions, poor quality of life (QOL), and unsatisfactory level of well-being. Resilience can be defined as a dynamic and amendable process, which maintains or improves life satisfaction and quick recovery from own dilemma. However, no meta-analysis of randomized controlled trials (RCTs) has thus far examined the effectiveness of resilience interventions among persons with neurocognitive disorders, and the results of RCTs were inconsistent. This systematic review aimed to assess the effectiveness of resilience interventions on psychosocial outcomes among persons with neurocognitive disorders.

Methods: Nine electronic Chinese and English databases (the Cochrane Library, PsycINFO, Web of Science, PubMed, Medline, Eric, JSTOR, CNKI, and WANGFANG) were searched through April 2021. Only RCTs were included, and the quality of the included studies was assessed by the Cochrane "Risk of Bias" tool. Meta-analysis was carried out on psychosocial outcomes, and heterogeneity was investigated by subgroup and sensitivity analysis. RevMan 5.4 was used for meta-analysis.

Results: Fourteen RCT studies were identified, representing a total of 2,442 participants with neurocognitive disorders. The risk of bias was high or unclear for most included studies in the domains of allocation concealment, blinding participants, and interventionists. Meta-analysis showed that heterogeneity was low or moderate. There were significant differences in favor of resilience interventions compared with control on the outcome of QOL, using the Quality of Life-Alzheimer Disease scale (QOL-AD) [$I^2 = 36\%$, standardized mean difference (SMD) $= 0.14$, 95% CI (0.02, 0.26), $p = 0.02$], and no significant differences on depression, using the Cornell Scale for Depression in Dementia (CSDD) [$I^2 = 41\%$, SMD $= -0.14$, 95% CI (-0.34, 0.05), $p = 0.16$], and neuropsychiatric symptoms using the Neuropsychiatric Inventory Questionnaire (NPI-Q) [$I^2 = 62\%$, SMD = −0.10, 95% CI (−0.37, −0.16), $p \leq 0.46$].

Conclusions: Resilience interventions had a significant benefit on QOL but no significant benefit on depression and neuropsychiatric behavioral symptoms. More evidence is needed to answer questions about how to implement resilience interventions and how to evaluate their effectiveness.

Keywords: resilience, intervention, meta-analysis, psychosocial outcomes, neurocognitive disorders

INTRODUCTION

Mild cognitive impairment (MCI), dementia, or Alzheimer's disease (following abbreviation neurocognitive disorders) are chronic progressive syndrome. During the phase transition process, divergent sections of the brain are affected, and a persons' capability of adaptation to the disease and environment gradually decreases (1). Neurocognitive disorders not only impair the person's memory, orientation, thinking, cognitive functioning, and language (2), but also trigger emotions and psychological symptoms, such as depression and anxiety (3, 4). In addition, the impact of neurocognitive disorders is long-lasting; it is extremely exacting or nearly impossible to be cured completely (5, 6). With these detrimental outcomes, neurocognitive disorders further lead to an unsatisfactory level of well-being and quality of life (QOL), such as physical function, and financial instability of individuals and families; these results also undermine people's ability to fulfill family, social, and professional roles (7). Neurocognitive disorders currently affected tens of millions of people all over the world and caused enormous medical and economic burdens. For example, there were 50 million people with dementia worldwide (2), and the number of people with dementia worldwide is projected to be 152 million in 2050 (8). Dementia contributes significantly to the global burden of disease, costing an estimated $818 billion annually (9), expected to reach $2 trillion by 2030 (8, 10–12). Thus, neurocognitive disorders are regarded as one of the greatest social, health, and economic challenges of the twenty-first century (8, 11–13). It is progressively crucial to develop strategies that facilitate and help persons with neurocognitive disorders to maintain independence, well-functioning, and high QOL in the long run.

There were various approaches to coping with the challenges affiliated with neurocognitive disorders. Resilience-centered interventions can be seen as one important approach to adapting to stress and reducing the adverse impact of the stressors (7). Luthar and Cicchetti (14) defined resilience as "a dynamic and amendable process," in which people use resources to acclimate to adversity (15). Meanwhile, Kunzler et al. (16) highlighted that resilience-centered interventions could be seen as the process of maintenance, withstanding, overcoming, adjustment, adaptation, posttraumatic growth, stress-related growth, rebound from a stressor, or rapid readjustment. As mentioned above, resilience can be defined as a process: after experiencing acute (short-run) or chronic (long-run) issues on health and stress, an individual can actively adapt, withstand, overcome, adjust, cope, and grow to maintain and improve his or her QOL with the support from multifaceted resources on individual and social levels.

The literature illustrated that protective factors of resilience were diverse, such as self-care, adherence to treatment programs, patient perceptions of pain and disease, adherence to physical activities, self-empowerment, health-related QOL, self-efficacy improvement, stress, depression, and anxiety reduction, optimism in viewpoints, and recovery acceleration (17–21). However, the process of resilience interventions focuses on reinforcing personal characteristics and exterior assets in response to a severe challenge to build an inclusive environment with multifaceted psychosocial supports (22). Similarly, other literature also suggested that resilience framework should include individual, family, community, and social components (23, 24). For example, Harris (24) stressed strengthening personal attributes in the process of resilience interventions, which could include self-acceptance of a person with neurocognitive disorders with the shifts in self, nurturing the individual's remaining competence, a positive perspective on diseases and dilemmas, and recognition of numerous means in which someone with dementia can contribute meaningly to their friends, family, and/or the community. Casey et al. (22) suggested five domains to implement resilience interventions: having a "fighting spirit" and personal control, maintaining solid family relationships, maintaining ties to communities, increasing awareness, addressing negative attitudes through dementia education, and engaging in physical activity. Kunzler et al. (16) suggested that resilience should include supportive doctors, linkages to helpful community groups and events, and sympathetic and supportive social surroundings. Overall, the literature mentioned above indicated that in the resilience process, multifaceted interventions should be taken, involving interactions between individuals and the external resources.

The outcomes of resilience-centered interventions are psychosocial, such as improving QOL, restoring normal performance, maintaining mental health, improving adaptability (25), better adjustment (26), enhancing mental well-being (27), reducing care dependence, good social relations, positive self-image (28), reducing burden or stress (27, 29), enhancing intent or meaning of life, and obtaining self-esteem, positive emotions, self-efficacy, boldness, active coping, optimism, social support, adaptation, and cognitive flexibility (including positive reassessment and acceptance) (16). However, one question arises regarding how to measure resilience-centered intervention outcomes in different resilience approaches. Windle et al. (30) studied tools for resilience interventions and concluded that the conceptual and theoretical adequacy of the scales was questionable, with no existing "gold standard" of resilience measures. Whelan et al. (15) indicated that key sets of outcomes for resilience in neurocognitive disorders have not been identified. For example, Ghanei Gheshlagh et al. (7) used three scales, which are Resilience Scale-25 (RS-25), Connor–Davidson Resilience Scale-10 (CDRISC-10), and Connor–Davidson Resilience Scale-25 (CDRISC-25), to assess the effectiveness of the resilience process for people with chronic physical diseases. Saint-Bryant et al. (26) used the Cornell Scale for Depression in Dementia (CSDD), Quality of Life Alzheimer's Disease scale (QOL-AD), and the Index of Relocation Adjustment Scale (IRA) to measure depression, QOL, and adjustment conditions as the outcomes of resilience process for older adults with dementia.

Another question is that the effect of resilience interventions is inconclusive. Thus far, there are only three systematic reviews (31–33) related to resilience interventions or outcome measures. Although Li et al. (31) claimed to contain resilience training, it was a mere strength training different from resilience. They also assessed cognitive outcomes, such as executive cognitive ability, global cognitive function, memory, and attention. Findings indicated positive effects on the executive cognitive capability and overall cognitive function, a weak-positive effect on memory, and no significance in attention. In the review of Carrion et al. (32), the resilience interventions focused on cognition-oriented caregiving approaches. The included 47 randomized controlled trials (RCTs) did not conduct a meta-analysis, and the results were inconclusive. In the review of Regan and Varanelli (33), the resilience interventions used modified cognitive behavior therapy (CBT) and problem-solving approach. They assessed three outcomes, including depression, anxiety, and adjustment in older adults with mild cognitive impairment and early dementia. The included seven RCTs and eight pre–post studies indicated positive effects in reducing depression in older persons with early dementia. However, Regan and Varanelli's (33) review did not conduct a meta-analysis, so it was unable to draw a clear conclusion about the intervention effect because of the divergent methods of the included studies. Additionally, the narrative review (15) identified five resilience interventions in three empirical studies of six papers, including Peer Support Network Services, Dementia Advisors, Memory Makers, Visual Arts Enrichment Activities, and Early-Stage and Beyond Community Activities. However, this narrative review included empirical studies, and the effectiveness of the resilience interventions could not be determined due to the study design.

Overall, there exist several dissimilarities regarding methodology and quality of studies among previous systematic reviews, which leads to inconsistent results regarding the effectiveness of resilience interventions. Currently, there is no systematic review that both includes RCT studies and conducts a meta-analysis. Therefore, this review aimed to identify RCT resilience interventions among persons with neurocognitive disorders to assess the effectiveness and provide further detailed evidence. This may contribute to enhancing existing resilience interventions and to facilitating the future development of such programs.

METHODS

Criteria for Considering Studies for This Review

Participants

Participants were people of all ages with neurocognitive disorders, including dementia, mild cognitive impairment (MCI), and Alzheimer's disease. Participants' formal diagnoses on types and severity of those neurocognitive disorders were based on corresponding scales, including the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (34); International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (35); or other comparable diagnostic criteria. We included people living in diverse settings, such as the community, hospitals, and nursing homes. We did not use a criterion for age so as not to exclude studies in which some participants were below 60 years old. If a mixed sample of participants (e.g., people with dementia and their caregivers) were found and the data of persons with dementia were reported separately or were collected by contacting the author, these studies also were included.

Interventions

Any intervention that promotes a person's state of adaptation and adjustment with the help of personal attributes and external assets, regardless of content, duration, setting, or mode of delivery, was included. Resilience, for example, can include active coping (e.g., planning, problem solving), self-efficacy, optimism or positive attributional style, cognitive flexibility (e.g., positive reassessment and acceptance of negative emotions and conditions), religiosity and spirituality (e.g., frequent religious visits), positive emotions or positive affect, hardiness, self-esteem, intent or meaning of life, sense of coherency (internal), locus of control, coping flexibility, hope, humor, altruism (16), physical strength training, formal or informal care, social connection, and community or other external resource support.

Studies were excluded if they involved animal trials and non-psychological or non-social interventions of resilience, such as pharmacological interventions (e.g., treatment with antidepressants).

Comparators

Comparators included no treatment, treatment as usual (TAU) (e.g., routine medication and usual social activities), and wait-list control. If the control group adopted active control, such as music, physical, and cognitive–behavioral, rather than no treatment, TAU, or wait-list control, the literature was excluded. For studies with two or more controls, our meta-analysis was conducted only using the control group of no treatment, TAU, or wait-list control.

Outcome Measures

We defined outcomes as assessments of psychosocial adaptation. For these outcomes, QOL was a primary outcome, and others were secondary outcomes, such as social relations, positive self-image, self-efficacy, hardiness, anxiety, and depression. We accepted all psychosocial assessment tools used in the included studies. Outcomes were assessed before the treatment, upon completion of the treatment, and follow-up evaluations to assess long-term effects. We considered measures self-assessed and scored by observers or clinicians.

Studies were excluded if the studies contained non-psychosocial outcomes of resilience, such as brain structure, immediate memory, attention and calculation, deferred memory, time orientation, location orientation, language, visual space, or the geographical environment. This ensured that the review focused on the psychosocial outcomes of resilience interventions. The absence of the outcome values was an exclusion criterion for this review: if the values of mean and standard deviation (SD) were not reported in the description of outcome, mean and SD cannot be obtained by contacting the authors, or mean and SD cannot be calculated by the review manager software or calculator provided by Cochran, the original study was deleted (Review manager software or calculator: https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-5-download; https://training.cochrane.org/resource/revman-calculator).

Types of Studies

Our review intended to include both published and unpublished RCTs in Chinese or English language. We also took into account cluster RCTs.

Electronic Searches

Nine electronic databases (the Cochrane Library, PsycINFO, Web of Science, PubMed, Medline, Eric, JSTOR, CNKI, and WANGFANG) were searched through April 2021. Gray literature was also searched from ProQuest Dissertations & Theses Database (PQDT) and DUXIU and reviewed. Authors of relevant conference abstracts were reached out for possible information sharing. The search terms used were the following: (a) dementia or Alzheimer or cognitive loss: MCI or dementia or Alzheimer or ADRD or "cognitive impai*" or "cognitive loss" or "cognitive decline"; (b) resilience or resiliency: resilien* OR adjust* OR adapt* OR "post-traumatic growth" OR "post-traumatic growth" OR "stress-related growth" OR withstand* OR overcom* OR resist* OR recover* OR thriv* OR adapt* OR adjust* OR bounc* back; and (c) RCT or random*. We used "subject OR title OR abstract OR keywords OR topic" to search. Search strategy was (MCI or dementia or Alzheimer or "cognitive impai*" or "cognitive loss" or "cognitive decline") AND (resilien* OR adjust* OR adapt* OR "post-traumatic growth" OR "post-traumatic growth" OR "stress-related growth" OR withstand* OR overcom* OR resist* OR recover* OR thriv* OR adapt* OR adjust* OR bounc* back) AND (RCT or random*).

Assessment of Risk of Bias in Included Studies

We employed the Cochrane "Risk of Bias" tool (36) to identify any risk of bias with a judgment of low risk, high risk, or unclear risk of bias for each study of the following areas: (1) selection bias, (2) random sequence generation, (3) allocation concealment, (4) blinding of participants and personnel, (5) blinding of outcome assessment, (6) incomplete outcome data, and (7) selective reporting.

Data Collection and Analysis

Studies Screening

Three reviewers (YW, YZH, and WCH) screened articles according to inclusion and exclusion criteria. Three reviewers independently reviewed the studies' title and abstract, then screened the full paper, and independently evaluated methodological quality. Any uncertainties concerning suitability were discussed at weekly group meetings with all reviewers.

Data Extraction

Three reviewers independently extracted data using a predesigned form from the included studies. The following data were extracted: (1) basic study information, namely, authors, reference, and country/region; (2) participant characteristics, namely, illness/condition, total number, and number in each group, age, gender, and race/ethnicity; (3) intervention characteristics, namely, intervention content, individual or group format, in-person or virtual, setting, length (e.g., number of weeks), number of sessions, duration per session, and control; (4) intervention assessment information, namely, time point (e.g., pretest, posttest, follow-up), measures, outcomes with screenshots (including the mean, standard deviation, and number of participants in each group at each time point), and outcome raters (e.g., patients, caregivers, and staff); and (5) information on bias risk assessment (see *Assessment of risk of bias in included studies*). After comparing results, any uncertainties that could not be solved were discussed in weekly meetings with all reviewers.

Data Analysis

RevMan 5.4 was used for meta-analysis. Meta-analysis was performed if outcomes were measured by the same scales in at least two studies. Heterogeneity was assessed using an I^2 statistic. To interpret heterogeneity, reviewers followed Cochrane guidance: 0–40% as not important, 30–60% as moderate heterogeneity, 50–90% as substantial heterogeneity, and 75–100% as considerable heterogeneity (37). A random-effects model was used if I^2 statistics reports the value of 50% or above. A fixed-effects model was used if I^2 statistics were lower than 50%. If one study used more than one instrument to measure the same outcome variable, the team employed the more commonly used instrument for the analysis.

Subgroup analyses were conducted with the following characteristics if applicable: outcome instrument, disease/conditions, country/region, rater, and follow-up. If the heterogeneity showed moderate or high, we performed subgroup and sensitivity analysis. Publication biases were assessed by a funnel plot if the number of studies used for meta-analysis was more than 10.

RESULTS

Search Results

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart of the study review and selection process. A total of 2,890 studies were searched from electronic searches. After deduplication, we considered a total of 2,885 studies. The remaining studies were screened at the title and abstract level based on the pre-established inclusion and exclusion criteria, depending on the study type, population, intervention, control, and outcome. Forty-five full papers were then reviewed, from which 31 were excluded utilizing the same criteria. Fourteen RCT studies satisfied all the inclusion criteria. Thus, 14 RCT studies representing a total of 2,442 participants with neurocognitive disorders were included in the systematic review and meta-analysis.

Included Study Characteristics

Location

Among 14 studies, 7 were conducted in the UK, 2 in the USA, 1 in Germany, 1 in Denmark, 1 in France, 1 in Netherlands, and 1 in Norway (**Table 1**).

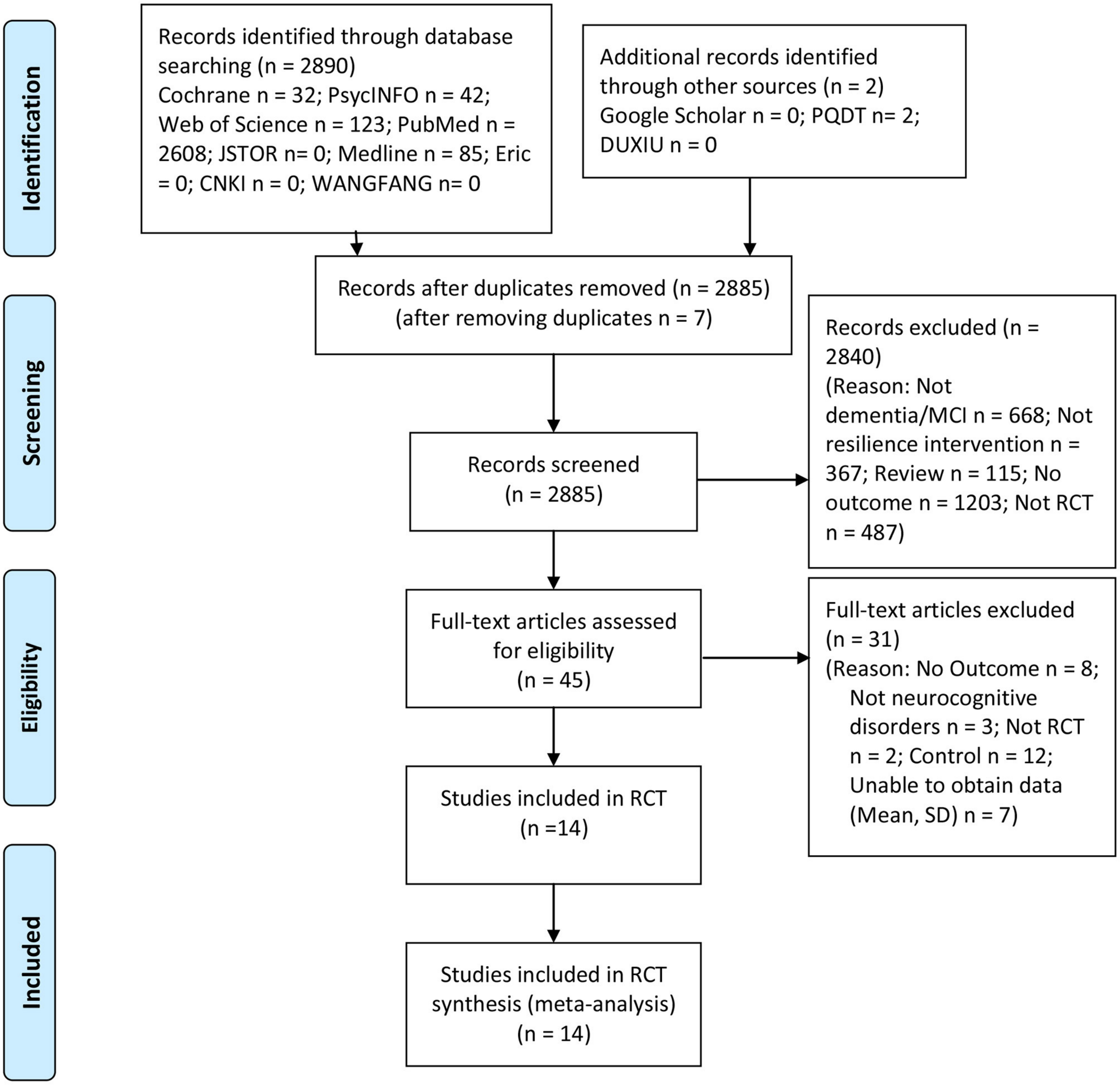


FIGURE 1 | Flowchart of the study selection process.

TABLE 1 | Characteristics of included studies.

Study Reference	Participants	Study Design	Intervention Group (IG)	Control Group (CG)	Outcome Measures	Data Collection Time and Raters	Results
Luttenberge et al. (38)	$N = 139$ (119 were analyzed); Mean age = 85 y/o; Residents with degenerative dementia from five German nursing homes	RCT	$N = 71$ (56 were analyzed) 6 months intervention comprised three segments: activities of daily living, motor stimulation, and cognitive stimulation (MAKS). Ten patients under the guidance of two therapists participated in the standardized intervention for 2 h, 6 days a week	$N = 68$ (63 were analyzed) Controls received treatment as usual	NOSGER (subscale: Mood, Social behavior, ADLs, IADLs)	Pre, post (6 months); Rated by nursing home staff	This effect was greatest on the social behavior ($p < 0.01$) and instrumental activity of daily living (IADLs) ($p = 0.01$)
Samus et al. (39)	$N = 303$ (265 with dementia, 38 with mild cognitive impairment; age $\geq$70 y/o, community-living, in Baltimore, MD, USA	RCT	$N = 110$ Care coordination intervention to systematically identify and address dementia-related caregiving according to people-centered caregiving planning; dementia education and skill-building strategies caregiving monitoring by an interdisciplinary team. Weekly in-person 2-h meetings	$N = 193$ Usual care	1. QOL-AD-participant 2. QOL-AD-proxy 3. ADRQL-40 4. NPI-Q 5. CSDD	Pre, post, f/u (9 months, 18 months); self-reported participants and masked evaluators	1. IG had a significant improvement in self-reported QOL 2. No group differences were found in neuropsychiatric symptoms, depression, or proxy-rated QOL QOL-AD-Self (18 months, $p = 0.027$); ADRQL-40 (18 months $p = 0.568$); QOL-AD-Informal (18 months, $p = 0.592$); CSDD (18 months $p = 0.925$); NPI-Q-Severity (18 months, $p = 0.233$)
Saint-Bryant et al. (26)	1. Dementia, $N = 19$; Mean age = 88 y/o; mild or moderate dementia 2. Staff participants, $N = 21$ Participants from care homes in the UK	RCT	$N = 10$ 1.The SettleIN program: staff-led; four required interventions: orientation, friends and family, identity, and lifestyle, and an optional intervention for residents that have difficulty engaging. Content included a range of activities designed to support the healthy adjustment 2. Four weeks for a full-time staff to complete, with a maximum of 6 weeks for part-time staff. Lasting 1 h and 15 min	$N = 9$ residential care as usual	1. CSDD 2. QOL-AD 3. IRA	Pre, post (week seven); Rated by staff participants	There was no significant difference regarding QOL, psychological well-being, or overall adjustment outcomes CSDD $p = 0.17$; QOL-AD $p = 0.43$; IRA $p = 0.24$
Waldorff et al. (40)	$N = 330$ Age $\geq$ 50 y/o, carers, and individuals with Alzheimer's disease, living in a nursing home, Denmark	RCT	$N = 167$, mean age: IG = 85.2, CG = 85.9); DAISY intervention: multifaceted and semitailored education, counseling, and support. All courses lasted 2 h; telephone approximately five to eight times every 3–4 weeks	$N = 163$ Routine follow-up	1. QOL-AD 2. NPI-Q 3. CDS (Cornell depression scale)	Pre, post, f/u (6 months, 12 month); Rated by trained raters	1. QOL-AD and NPI-Q outcome did not have any significant effect at 12 months 2. Non-significant but a small difference was observed for CDS in favor of IG ($p = 0.0146$ and $p = 0.0103$, respectively)

(Continued)

TABLE 1 | Continued

Study Reference	Participants	Study Design	Intervention Group (IG)	Control Group (CG)	Outcome Measures	Data Collection Time and Raters	Results
Surr et al. (41)	$N = 726$ (intervention group: mean age = 86 y/o, controls mean age = 85 y/o); permanent resident of the care home, officially diagnosed with dementia, in care homes in the UK	RCT	$N = 418$ dementia, $N = 31$ care homes Adhered to standard procedures specified in the DCM Dementia Care Mapping^{TM}) manual and guidelines in the provision of individualized person-centered care including five components, such as observation, reporting, feedback, and action planning; 38 min a time, session 1–2 weeks	$N = 308$ dementia $N = 19$ care homes, usual care	1. CMAI 2. NPI 3. QOL-AD 4. PAS	Pre, post, f/u (6 months,16 months); Rated by independent researchers	1. CMAI was lower in IG than in CG ($p = 0.104$ 2. NPI, PAS, and QOL-AD outcomes were not clinically effective at reducing agitation or improving QOL and other outcomes
Jha et al. (27)	$N = 48$ (34 people completed the trial) people with MCI and early dementia and their family carers from villages in Hertfordshire in the UK Age $\geq$ 65 y/o	RCT	$N = 17$ Recovery-orientated psychiatric therapeutic: three components: (a) prediagnostic counseling and well-being assessment; (b) therapeutic diagnostic consultation; (c) written feedback. lasting at least an hour for 6 months	$N = 17$ Control group (treatment, as usual, TAU)	1. WHO-5 2. CSDD 3. EQ-5D 4. ZBI	Pre, post (6 months); Rated by the clinician	IG exhibited a significant enhancement in the WHO Well-being Index ($p = 0.03$). There were also trends of improvement in other outcome measures WHO-5 ($p = 0.03$) CSDD ($p = 0.38$) EQ-5D ($p = 0.66$) ZBI ($p = 0.90$)
Vickrey et al. (42)	$N = 408$ dyads 408 patients with dementia age $\geq$65 y/o paired with 408 informal caregivers. Three health care organizations in collaboration with 3 community agencies in southern California, USA	RCT	$N = 238$ dyads 1. A dementia guideline-based disease management program for more than 12 months 2. Dementia care managers (mostly social workers) employed a web-based care management software system for care planning and coordination 3. The care management protocol included ongoing follow-up, usually via phone, with a needs-based frequency and a formal reassessment every 6 months to assess the need for major revisions to the caregiving plan 4.At each intervention clinic, over 90 min of standardized, interactive seminars (in up to 5 sessions)	$N = 170$ dyads Usual Care	1. Receipt of community resources 2. HUI3	Pre, post, f/u (12–18months); Rated by caregivers	1. Higher proportions received community agency assistance ($p = 0.03$) than those who received usual care 2. Patient health-related QOL, caregiving quality, overall quality of patient care, level of unmet caregiving assistance needs, and social support were better for IG than CG ($p = 0.05$)
Dechamps (43)	$N = 160$ Age: 65–102 y/o, mean = 82.3 Neuropsychiatric diagnosis as dementia and psychosis; from the long-term care home and the nursing homes, France	RCT	Exercise regimen/activity program 1. Adapted Tai Chi (AT): $N = 51$ Exercise program: 4 sessions of 30 min a week for 6 months 2. the Cognition-Action program (CA): $N = 49$ CA is a training program to enhance adhesion to exercise by adding a meaning to exercise: 30 min and advanced to 40 min twice a week for 6 months	$N = 60$ Usual care	1. GDS 2. NPI 3. ADL	Pre, post, f/u (6 and 12 months); Rated by researchers	1. ADL score has no significance (AT: $p = 0.24$ and CA: $p = 0.15$) 2. NPI was unchanged or improved in the intervention groups ($p > 0.001$) 3. Neuropsychiatric diagnosis subgroups did not respond to any interventions

(Continued)

TABLE 1 | Continued

Study Reference	Participants	Study Design	Intervention Group (IG)	Control Group (CG)	Outcome Measures	Data Collection Time and Raters	Results
Lowery et al. (44)	$N = 131$ dyads 1. Control mean age = 78 y/o 2. Intervention mean age = 79 y/o 3. Participants with dementia living home from Diseases Research Network's dementia research register from the North Thames, in the UK	RCT	Exercise regimen/activity program $N = 64$ Exercise regimen in addition to TAU (treatment) Customized walking regimen designed to gradually become intensive and last from 20 to 30 min, at least five times a week	$N = 67$ Treatment as usual	1. DemQOL-Proxy 2. NPI	Pre, post, f/u (6, 12 weeks); Rated by the research worker	1. No significant difference was found between the groups of mean NPI (6 weeks: $p = 0.76$;12 weeks: $p = 0.6$) 2. No statistically significant differences between the groups in QOL of participants with dementia (measured using the Demqol-proxy) (6 weeks: $p = 0.49$;12 weeks: $p = 0.09$)
Henskens et al. (28)	$N = 87$ Age ≥65 y/o 87 residents with dementia living in a psychogeriatric ward of nursing home (NH), Amsterdam, the Netherlands	RCT	Exercise regimen/activity program $N = 43$ ADL training, a multicomponent aerobic and strength exercise training, and combined ADL and exercise training. Receive three 3-h educational sessions. strength and aerobic exercises, with a frequency of three times a week, 30–45 min each session. Sessions rotated weekly, consisting of two strength sessions and one aerobic session, followed by a week of two aerobic sessions and one strength session. Subgroups: 1. the exercise (physical activity) PADL; 2. the exercise (physical activity) PCO	$N = 44$ Care-as-usual Subgroups: 1. Social activity SADL 2. Social activity SCO	1. CDS (the Care Dependency Scale) 2. E-ADL 2. Qualidem (subscale: care relationship; positive affect; negative affect; restless tense behavior; positive self-image; social relations; social isolation; feeling at home; having something to do	Pre, post, f/u (3 and 6 months); rated by physiotherapists	1.The ADL training positively affected overall QOL ($p = 0.004$) and its multiple aspects: care relationship ($p = 0.004$), positive self-image ($p = 0.002$), and feeling at home ($p = 0.001$) compared to care-as-usual 2. No benefits were observed of exercise on QOL 3. No benefits were observed from a combined ADL and exercise interventions on QOL 4. No effects were found of the three-movement interventions on ADL performance
Jøranson et al. (45)	$N = 60$, age range 62–95 y/o residents with dementia or cognitive impairment in 10 nursing home units, Norway	RCT	Exercise regimen/activity program $N = 27$ A robot-aided group activity with the robot seal Paro Group sessions in a separate room for 30 min twice a week for 12 weeks	$N = 26$ treatment as usual	1. BARS 2. CSDD	Pre, post, f/u (12 weeks, 3 months) Rated by staff	There were statistically significant differences in changes in agitation and depression between groups from T0 to T2. No significant differences in changes on agitation or depression between groups from T0 to T1 T1–T0: BARS: $p = 0.098$; CSDD: $p = 0.098$ T2–T0: BARS: $p = 0.048$; CSDD: $p = 0.028$

(Continued)

TABLE 1 | Continued

Study Reference	Participants	Study Design	Intervention Group (IG)	Control Group (CG)	Outcome Measures	Data Collection Time and Raters	Results
Churcher Clarke et al. (29)	$N = 31$, age range 61–95 y/o; people with dementia; From care homes in the UK	RCT	$N = 20$ A group-based adapted mindfulness intervention plus treatment as usual: a 10-session intervention, comprising 10, 1-h group sessions, running twice per week for 5 weeks at the care home	$N = 11$ Treatment as usual	1. CSDD 2. RAID 3. QOL-AD 4. PSS-13	Pre, post (1week postintervention) Rated by patients	There was a significant improvement in QOL in IG compared to CG ($p = 0.05$). No significant changes in other outcomes
Woods et al. (46)	$N = 488$ Mean age = 77.5 y/o individuals with mild to moderate dementia living in family homes in the UK	RCT	$N = 268$ Joint reminiscence, 12 consecutive weeks + monthly maintenance sessions for an additional 7 months. Twelve 2-h weekly sessions	$N = 219$ Usual care	QOL-AD	Pre, post, f/u (3 months, 10 months); self-reported	No differences in outcome between the IG and CG at the 10-month endpoint ($p = 0.53$)
Ali et al. (47)	$N = 40$ dyads Carer and individual with dementia from communities Age $\geq$40 y/o, in the UK	RCT	$N = 20$ dyads 1. Dementia individual cognitive stimulation therapy (iCST arm) and treatment as usual 2. 40 sessions over 20 weeks: warm-up, orientation, the main activity) twice a week for 30 min per session	$N = 20$ dyads A waiting list control group received treatment as usual	QOL-AD	Baseline, midpoint (week 11), the end (week 21) Rated by the research assistant	QOL was significantly higher in the iCST arm at 21 weeks (week 11 $p = 0.61$; week 21 $p = 0.02$)

QOL-AD, Quality of Life–Alzheimer Disease scale; QOL-AD-participant, Quality of Life in AD, which was administered to participants; QOL-AD-proxy, Quality of Life in AD for study partners; DemQOL-Proxy, quality of life of participants with dementia; DQOL, Dementia Quality of Life instrument.; ADRQL-40, the Alzheimer's Disease Rated Quality of Life-40 item scale; EQ-5D, EUROQOL; WHO-5, WHO Well-Being Index; GAS, Goal Attainment Scale; NOSGER, the Nurses' Observation Scale for Geriatric Patients (subscale including: Mood, Social behavior, ADLS, IADL); Qualidem assesses QOL and subscales including (1) care relationship, (2) positive affect, (3) negative affect, (4) restless tense behavior, (5) positive self-image, (6) social relations, (7) social isolation, (8) feeling at home, (9) having something to do; GDS, Geriatric Depression Scale; CDS, Cornell depression scale; CSDD, the Cornell Scale for Depression in Dementia; CS, Cornell scale for depression in dementia; ABID, Agitated Behaviors in Dementia scale; BARS, the Brief Agitation Rating Scale; CMAI, Cohen-Mansfield Agitation Inventory; PAS, the Pittsburgh Agitation Scale; RAID, the Rating Anxiety in Dementia Scale; NPI, Neuropsychiatric Inventory; NPI-Q, the Neuropsychiatric Inventory questionnaire; IRA, the Index of Relocation Adjustment; PSS-13, Perceived Stress Scale; ZBI, Zarit Burden Interview; CDS, Care Dependency Scale; HUI3, the Health Utilities Index Mark 3; IADL, instrumental activities of daily living; ADL, activities of daily living; E-ADL, Assessors of the Erlangen ADL.

Participants

Participants in most studies ($n = 10$) were persons with dementia (26, 28, 29, 38, 41–44, 46, 47), one as persons with MCI (39), one as persons with MCI and early dementia (27), one as persons with dementia or cognitive impairment (45), and one was Alzheimer's (40). The number of participants ranged from 19 to 726, and seven studies had more than 100 participants. Participants were recruited from communities ($n = 6$) and nursing homes/residential care facilities ($n = 8$).

Interventions

We identified six resilience approaches based on content descriptions, including integrated approaches ($n = 5$), exercise regimen or activity programs ($n = 4$), psychological interventional technique ($n = 2$), a psychiatric intervention ($n = 1$), disease/case management ($n = 1$), and cognitive stimulation therapy ($n = 1$). Among five studies with integrated approaches, one was individualized person-centered care provided by standard procedures to diminish turmoil in care home residents with dementia (41), one was multimodal non-drug therapy on dementia's symptom and care need (38), one was multidimensional home-based care coordination provided by an interdisciplinary team to maximize independence for persons with MCI living home (39), one was a staff-led intervention that comprises four mandatory modules and one optional module to facilitate the adaptation of seniors with dementia after placement into residential care (26), and one was a psychosocial intervention including multifaceted and semi-tailored counseling, education, and support (40).

Four studies provided exercise regimens or activity programs (28, 43–45), such as adapted Tai Chi and cognition-action program, walking, aerobic, and strength exercise training. Two mental interventional techniques used mindfulness (29) and reminiscence (46). One study of recovery-orientated psychiatric intervention packages included prediagnostic well-being assessment and counseling, diagnostic consultation with written feedback, and postdiagnostic support (27). One disease management employed an internet-based care management software system for care planning and coordination (42). One individual cognitive stimulation therapy intervened and assessed adaptive functioning and QOL of participants with dementia (47). All interventions were conducted in groups of persons older than 40 years old.

Regarding intervention intensity, the length ranged from 6 weeks to 12 months. The duration of sessions included 30 min twice a week ($n = 2$), 40 min twice a week ($n = 1$), 30–45 min once a week ($n = 1$), 38 min once per 1–2 weeks ($n = 1$), 20–30 min at least five times per week ($n = 1$), 1 h at least once a week ($n = 4$), and 2 h, 6 days a week ($n = 4$).

Comparators

Control groups included usual care or TAU ($n = 12$), routine follow-up ($n = 1$) (40), and a wait-list control group ($n = 1$) (47).

Outcome Measurement

Table 1 shows that 14 studies assessed psychosocial outcomes, including QOL, well-being, mood state, neuropsychiatric symptom, positive self-image, adaption, goal attainment, and adjustment. Most studies evaluated QOL ($n = 11$). Specifically, QOL was rated by seven scales [Quality of Life in Alzheimer Disease (QOL-AD-participant), Quality of Life in A.D. for study partners (QOL-AD-proxy), quality of life of participants with dementia (DemQOL-Proxy), Dementia Quality of Life instrument (DQOL), the Alzheimer's Disease Rated Quality of Life-40 item scale (ADRQL-40), EUROQOL (EQ-5D), the Health Utilities Index Mark 3 (HUI3), and QOL-AD] in 11 studies. Mental well-being was rated by one scale [WHO Well-being Index (WHO-5)] in one study. Adaption was rated by three scales [Perceived Stress Scale (PSS-13), Zarit Burden Interview (ZBI), and Cornell depression scale (CDS)] in three studies. Goal attainment was rated by one scale [Goal Attainment Scale (GAS)] in one study. Adjustment was rated by one scale (IRA) in one study. Mood state was assessed by 11 scales, including depression [Geriatric Depression Scale (GDS), Cornell Scale for Depression in Dementia (CS), CDS, and CSDD] in seven studies, agitation [Agitated Behaviors in Dementia scale (ABID), the Brief Agitation Rating Scale (BARS), Cohen–Mansfield Agitation Inventory (CMAI), and the Pittsburgh Agitation Scale (PAS)] in three studies, and anxiety [the Rating Anxiety in Dementia Scale (RAID)] in one study. Neuropsychiatric symptom was rated by two scales [Neuropsychiatric Inventory (NPI) and the Neuropsychiatric Inventory questionnaire (NPI-Q)] in five studies. In addition, resilience was rated in two studies by two comprehensive scales [Qualidem and the Nurses' Observation Scale for Geriatric Patients (NOSGER)], including positive self-image, social relations, and mood.

All 14 studies had pre- and postintervention assessments. Eleven studies had follow-up (f/u) assessments, and the f/u assessments were conducted at different time points (e.g., 7, 12, and 21 weeks and 3, 6, 10, 12, 16, and 18 months).

Effects of Interventions

Overall, the effects of resilience interventions were diverse in various outcomes. In terms of social behavior, one study indicated significant differences in favor of resilience interventions compared with controls (38). Meanwhile, no significant differences were found in neuropsychiatric symptoms (39–41, 43, 44), adjustment (26), stress (29), and anxiety (29) in favor of resilience interventions compared with controls. Besides, the results of other outcomes' assessments were inconsistent. Specifically, regarding QOL, seven studies showed no statistical significance in favor of resilience interventions compared with controls (26, 27, 40–42, 44, 46), while two showed a significant effect (29, 47). One showed a significant enhancement in self-reported QOL but no significant improvement in proxy-rated QOL (39). One showed that activities of daily living (ADL) training had positively affected overall QOL, but no benefits were observed for exercise on QOL (28). As for depression, four included studies showed that the resilience interventions were not statistically different compared with controls (27, 29, 39, 40), while one showed statistically significant differences (45). In terms of well-being, one study showed no significance in favor of resilience interventions compared with controls (26), while the other study showed statistical significance (27). About the effects on agitation, one showed no significance in favor of resilience interventions compared with controls (41), while one showed statistical significance (45).

Risk of Bias

Risks of bias are summarized in **Figure 2**. The main flaws for risks of bias across 14 studies were in allocation concealment and blinding participants and interventionists. Regarding random sequence generation, 13 studies were judged to be at low risk, which used computer-generated random numbers, a block randomization method, a custom Excel program, or a web-based system.

For allocation concealment, five studies were rated as low risk, which used sealed envelopes, allocation numbers by a blind assigner, or emphasis on allocation concealment. Five studies were judged to be high risk, which reported no concealment in the allocation process. The remaining four studies did not report information on allocation concealment and were rated as unclear.

Regarding blinding participants and interventionists, 3 studies were rated as low risk, 10 studies as high risk, and 1 study as unclear. Meanwhile, most studies (n = 13) were judged as low risk for blinding outcome assessment, by using personnel not included in the intervention process, and one study was judged as high risk due to non-blinding outcome assessment.

All studies were judged to be at low risk for incomplete outcome data because the dropout rate was low (<30%) during the intervention, and they explained the numbers and reasons for dropout and the data analysis methods of dealing with missing values. Lastly, all studies were judged as low risk for selective reporting.

Meta-Analysis Results for Quality of Life

Meta-Analysis

Seven studies reported data on quality of life, assessed by QOL-AD and were pooled for a meta-analysis using a fixed-effects model. Results illustrated that there were significant standardized mean differences in favor of resilience interventions compared with controls for QOL [SMD = 0.14, 95% CI (0.02, 0.32), $p = 0.02$] (**Figure 3**).

Subgroup Analyses

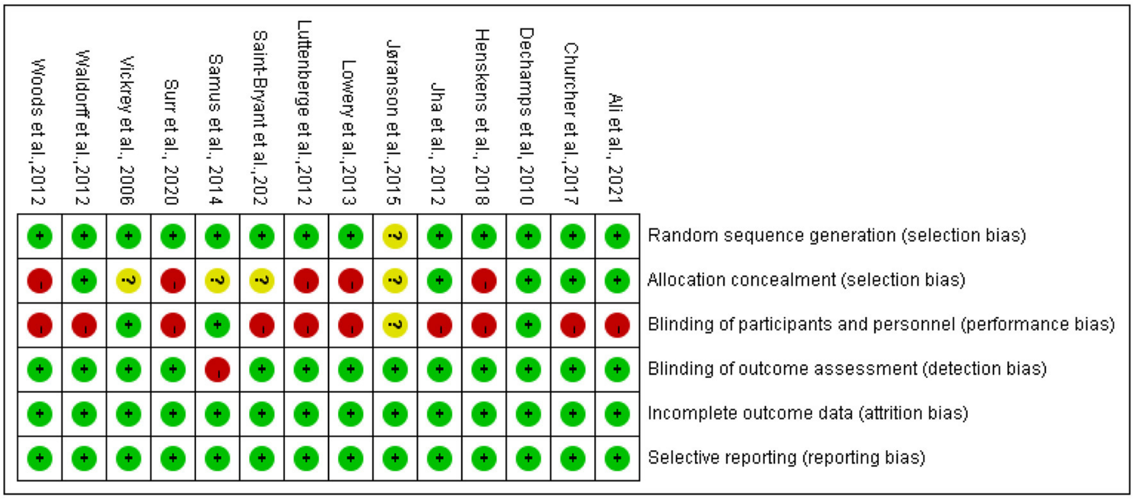
We further performed subgroup analyses with results shown in **Figure 4**. The subgroup result of the studies of the f/u assessments with 6 months showed significant standardized mean differences in favor of controls compared with resilience interventions [SMD = −0.21, 95% CI (−0.38, −0.03), $p = 0.02$] and no heterogeneity ($I^2 = 0\%$). The subgroup result of the studies of outcome rated by patients showed significant standardized mean differences in favor of resilience interventions compared with controls [SMD = 0.14, 95% CI (0.01, 0.27), $p = 0.03$] and no heterogeneity ($I^2 = 0\%$). Other subgroup result analyses showed no significant standardized mean differences in favor of resilience interventions compared with controls, and moderate heterogeneity (I^2 = 36%−41%), which included the subgroup of the studies of persons with dementia [SMD = 0.14, 95% CI (−0.03, 0.30), $p = 0.11$], the subgroup of the studies of approaches using integrated approaches [SMD = 0.11, 95% CI (−0.04, 0.25), $p = 0.16$], and the subgroup of the studies conducted in the UK [SMD = 0.14, 95% CI (−0.03, 0.30), $p = 0.11$].

Assessment of Sensitivity

The heterogeneity of the seven included studies was moderate ($I^2 = 36$, $\text{chi}^2 = 9.41$), which suggested that heterogeneity might not be important as explained in Cochrane guidance. The sensitivity analysis showed no heterogeneity ($I^2 = 0\%$ $\text{chi}^2 = 4.55$) after a small sample study ($n = 40$) (47) was deleted (see **Figure 5**).

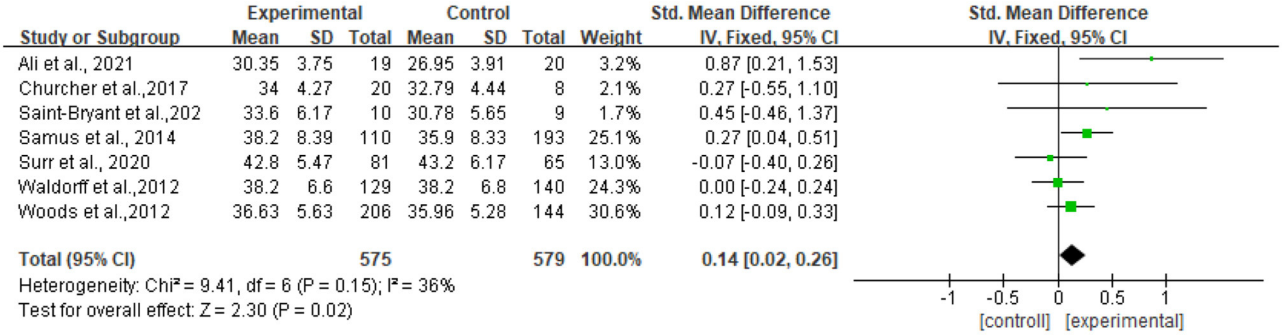
Analysis of Publication

Only seven RCTs were included, so the funnel plot was not made, but publication bias may exist.



	Woods et al.,2012	Waldorff et al.,2012	Vickrey et al., 2006	Surr et al., 2020	Samus et al., 2014	Saint-Bryant et al.,202	Luttenberge et al.,2012	Lowery et al.,2013	Jøranson et al.,2015	Jha et al., 2012	Henskens et al., 2018	Dechamps et al, 2010	Churcher et al.,2017	Ali et al., 2021
Random sequence generation (selection bias)	+	+	+	+	+	+	+	+	?	+	+	+	+	+
Allocation concealment (selection bias)	-	+	?	-	?	?	-	-	?	+	-	+	+	+
Blinding of participants and personnel (performance bias)	-	-	+	-	+	-	-	-	?	-	-	+	-	-
Blinding of outcome assessment (detection bias)	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+

FIGURE 2 | Risk of bias summary.



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ali et al., 2021	30.35	3.75	19	26.95	3.91	20	3.2%	0.87 [0.21, 1.53]
Churcher et al.,2017	34	4.27	20	32.79	4.44	8	2.1%	0.27 [-0.55, 1.10]
Saint-Bryant et al.,202	33.6	6.17	10	30.78	5.65	9	1.7%	0.45 [-0.46, 1.37]
Samus et al., 2014	38.2	8.39	110	35.9	8.33	193	25.1%	0.27 [0.04, 0.51]
Surr et al., 2020	42.8	5.47	81	43.2	6.17	65	13.0%	-0.07 [-0.40, 0.26]
Waldorff et al.,2012	38.2	6.6	129	38.2	6.8	140	24.3%	0.00 [-0.24, 0.24]
Woods et al.,2012	36.63	5.63	206	35.96	5.28	144	30.6%	0.12 [-0.09, 0.33]
Total (95% CI)			**575**			**579**	**100.0%**	**0.14 [0.02, 0.26]**

Heterogeneity: Chi² = 9.41, df = 6 (P = 0.15); I² = 36%

Test for overall effect: Z = 2.30 (P = 0.02)

FIGURE 3 | Effect size of the intervention group vs. the control group on QOL-AD rating scores.

Meta-Analysis Results for Depression

Meta-Analysis

Five studies reported data on depression assessed by the CSDD and were pooled for a meta-analysis using a fixed-effects model. Results demonstrated that there were no significant standardized mean differences in favor of resilience interventions compared with controls for depression [SMD = −0.14, 95% CI (−0.34, 0.05), $p = 0.16$] (**Figure 6**).

Subgroup Analyses

Figure 7 shows that no significant standardized mean differences in favor of resilience interventions compared with controls for CSDD were found in subgroup analyses. The heterogeneity ranged from 0 to 83%. Specifically, the subgroup result of participants with dementia showed no heterogeneity ($I^2 = 0\%$). Other subgroup results showed moderate or high heterogeneity ($I^2 = 53\% - 83\%$).

Assessment of Sensitivity

The heterogeneity of the five included studies was moderate ($I^2 = 41$ chi$^2 = 6.77$). The sensitivity analysis showed that the heterogeneity decreased ($I^2 = 0\%$ chi$^2 = 1.26$) after a small sample study ($n = 19$) (26) was deleted (see **Figure 8**).

Analysis of Publication Bias

Only five RCTs were included, so the funnel plot was not made, but publication bias may exist.

Meta-Analysis Results for Neuropsychiatric Symptoms

Meta-Analysis

Two studies reported data on neuropsychiatric symptoms assessed by NPI-Q and were pooled for a meta-analysis using the random-effects model. Results revealed that there were no significant standardized mean differences in favor of resilience interventions compared with controls for neuropsychiatric symptoms [SMD = −0.10, 95% CI (−0.37, −0.16), $p = 0.46$] (**Figure 9**). Meanwhile, there tended to be substantial heterogeneity in the two included studies ($I^2 = 62\%$, chi$^2 = 2.62$).

Analysis of Publication Bias

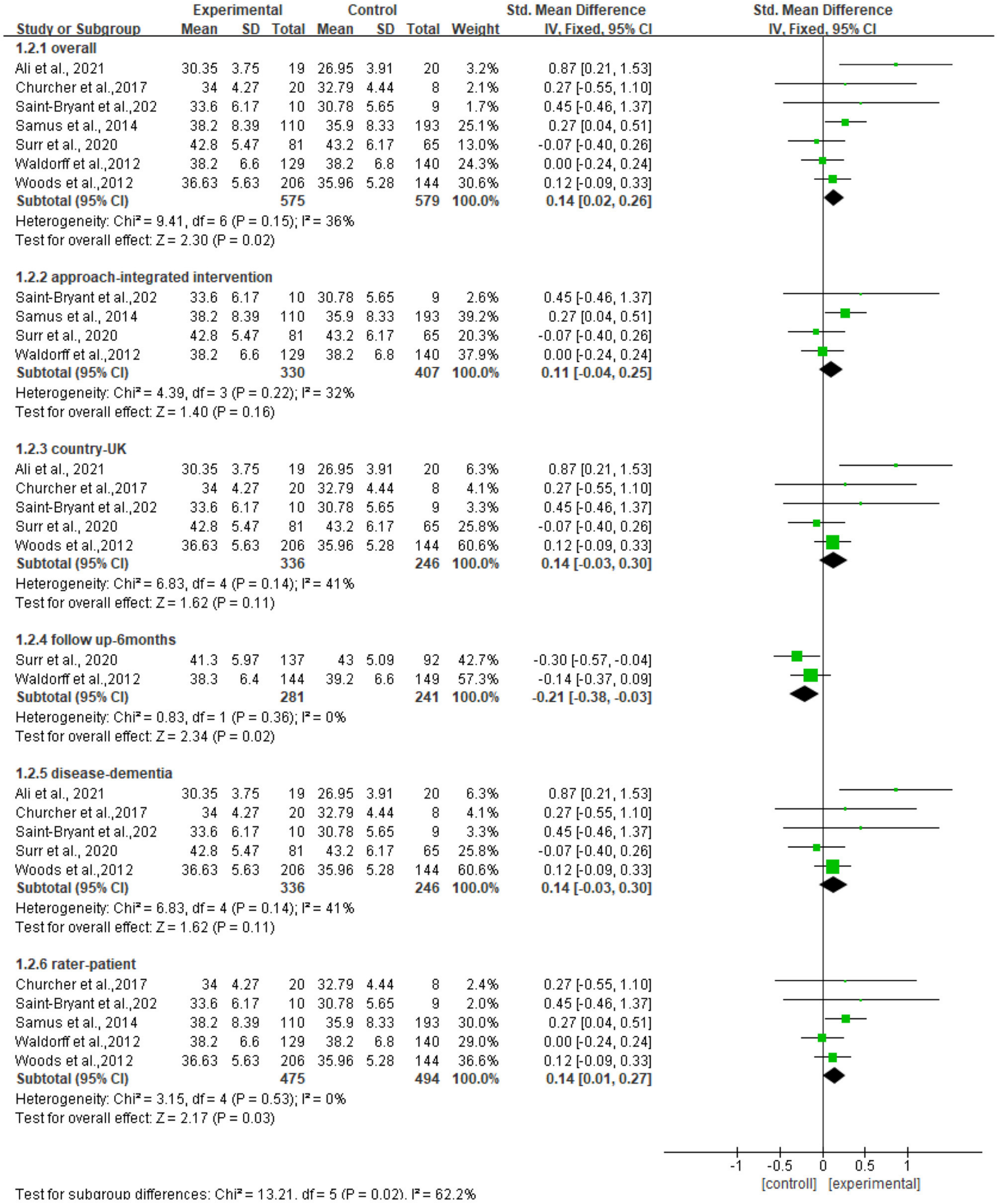
Only two RCTs were included, so the funnel plot was not made, but publication bias may exist.

DISCUSSION

This systematic review and meta-analysis examined the effectiveness of resilience interventions among persons with neurocognitive disorders. A total of 14 RCT studies representing 2,442 participants were identified that fulfilled the inclusion criteria of this review. The risk of bias was either high or unclear for most studies in allocation concealment, blinding participants, and interventionists domains. Meta-analyses were conducted for a primary outcome of QOL and secondary outcomes of depression and neuropsychiatric symptoms. Our results indicated that resilience interventions had a significant positive effect on persons with neurocognitive disorders in enhancing QOL but might not be beneficial in decreasing depression and neuropsychiatric symptoms. Meanwhile, many other psychosocial outcomes were measured less frequently.

Our review identified target groups of neurocognitive disorders based on various conditions including symptoms and level of severities: mild or moderate dementia, cognitive impairment or MCI, and Alzheimer's disease. Similarly, specific target groups in the review of Regan and Varanelli (33) included mild cognitive impairment and early dementia. Inconsistent with our study, some other reviews (31, 32) focused on mixed target groups, including both healthy older adults and older adults at risk of dementia, MCI, and Alzheimer's disease, focusing on the early prevention and intervention of neurocognitive disorders. This might also be one reason why it was impossible to judge the effect of interventions due to sample heterogeneity.

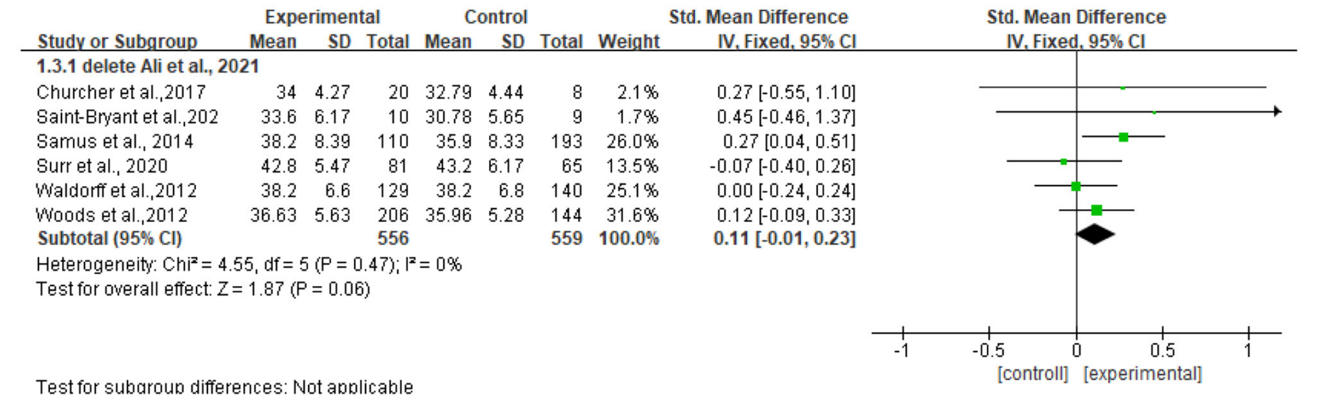
Meanwhile, our review included RCTs and conducted meta-analyses to assess the effect of resilience interventions. Consistent with our study, two previous systematic reviews also contained RCTs, which included 12 RCTs (31) and 47 RCTs (32), respectively. However, they applied a narrative approach to synthesize the findings without conducting a meta-analysis. Inconsistent with our study, the review of Regan et al. (33) included other study designs, such as pre–post studies, besides RCTs, which might be one of the reasons why the findings



	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
1.2.1 overall								
Ali et al., 2021	30.35	3.75	19	26.95	3.91	20	3.2%	0.87 [0.21, 1.53]
Churcher et al.,2017	34	4.27	20	32.79	4.44	8	2.1%	0.27 [-0.55, 1.10]
Saint-Bryant et al.,202	33.6	6.17	10	30.78	5.65	9	1.7%	0.45 [-0.46, 1.37]
Samus et al., 2014	38.2	8.39	110	35.9	8.33	193	25.1%	0.27 [0.04, 0.51]
Surr et al., 2020	42.8	5.47	81	43.2	6.17	65	13.0%	-0.07 [-0.40, 0.26]
Waldorff et al.,2012	38.2	6.6	129	38.2	6.8	140	24.3%	0.00 [-0.24, 0.24]
Woods et al.,2012	36.63	5.63	206	35.96	5.28	144	30.6%	0.12 [-0.09, 0.33]
Subtotal (95% CI)			**575**			**579**	**100.0%**	**0.14 [0.02, 0.26]**
Heterogeneity: Chi² = 9.41, df = 6 (P = 0.15); I² = 36%								
Test for overall effect: Z = 2.30 (P = 0.02)								
1.2.2 approach-integrated intervention								
Saint-Bryant et al.,202	33.6	6.17	10	30.78	5.65	9	2.6%	0.45 [-0.46, 1.37]
Samus et al., 2014	38.2	8.39	110	35.9	8.33	193	39.2%	0.27 [0.04, 0.51]
Surr et al., 2020	42.8	5.47	81	43.2	6.17	65	20.3%	-0.07 [-0.40, 0.26]
Waldorff et al.,2012	38.2	6.6	129	38.2	6.8	140	37.9%	0.00 [-0.24, 0.24]
Subtotal (95% CI)			**330**			**407**	**100.0%**	**0.11 [-0.04, 0.25]**
Heterogeneity: Chi² = 4.39, df = 3 (P = 0.22); I² = 32%								
Test for overall effect: Z = 1.40 (P = 0.16)								
1.2.3 country-UK								
Ali et al., 2021	30.35	3.75	19	26.95	3.91	20	6.3%	0.87 [0.21, 1.53]
Churcher et al.,2017	34	4.27	20	32.79	4.44	8	4.1%	0.27 [-0.55, 1.10]
Saint-Bryant et al.,202	33.6	6.17	10	30.78	5.65	9	3.3%	0.45 [-0.46, 1.37]
Surr et al., 2020	42.8	5.47	81	43.2	6.17	65	25.8%	-0.07 [-0.40, 0.26]
Woods et al.,2012	36.63	5.63	206	35.96	5.28	144	60.6%	0.12 [-0.09, 0.33]
Subtotal (95% CI)			**336**			**246**	**100.0%**	**0.14 [-0.03, 0.30]**
Heterogeneity: Chi² = 6.83, df = 4 (P = 0.14); I² = 41%								
Test for overall effect: Z = 1.62 (P = 0.11)								
1.2.4 follow up-6months								
Surr et al., 2020	41.3	5.97	137	43	5.09	92	42.7%	-0.30 [-0.57, -0.04]
Waldorff et al.,2012	38.3	6.4	144	39.2	6.6	149	57.3%	-0.14 [-0.37, 0.09]
Subtotal (95% CI)			**281**			**241**	**100.0%**	**-0.21 [-0.38, -0.03]**
Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%								
Test for overall effect: Z = 2.34 (P = 0.02)								
1.2.5 disease-dementia								
Ali et al., 2021	30.35	3.75	19	26.95	3.91	20	6.3%	0.87 [0.21, 1.53]
Churcher et al.,2017	34	4.27	20	32.79	4.44	8	4.1%	0.27 [-0.55, 1.10]
Saint-Bryant et al.,202	33.6	6.17	10	30.78	5.65	9	3.3%	0.45 [-0.46, 1.37]
Surr et al., 2020	42.8	5.47	81	43.2	6.17	65	25.8%	-0.07 [-0.40, 0.26]
Woods et al.,2012	36.63	5.63	206	35.96	5.28	144	60.6%	0.12 [-0.09, 0.33]
Subtotal (95% CI)			**336**			**246**	**100.0%**	**0.14 [-0.03, 0.30]**
Heterogeneity: Chi² = 6.83, df = 4 (P = 0.14); I² = 41%								
Test for overall effect: Z = 1.62 (P = 0.11)								
1.2.6 rater-patient								
Churcher et al.,2017	34	4.27	20	32.79	4.44	8	2.4%	0.27 [-0.55, 1.10]
Saint-Bryant et al.,202	33.6	6.17	10	30.78	5.65	9	2.0%	0.45 [-0.46, 1.37]
Samus et al., 2014	38.2	8.39	110	35.9	8.33	193	30.0%	0.27 [0.04, 0.51]
Waldorff et al.,2012	38.2	6.6	129	38.2	6.8	140	29.0%	0.00 [-0.24, 0.24]
Woods et al.,2012	36.63	5.63	206	35.96	5.28	144	36.6%	0.12 [-0.09, 0.33]
Subtotal (95% CI)			**475**			**494**	**100.0%**	**0.14 [0.01, 0.27]**
Heterogeneity: Chi² = 3.15, df = 4 (P = 0.53); I² = 0%								
Test for overall effect: Z = 2.17 (P = 0.03)								

Test for subgroup differences: Chi² = 13.21, df = 5 (P = 0.02), I² = 62.2%

FIGURE 4 | Subgroup analyses of the intervention group vs. the control group on QOL-AD rating scores.

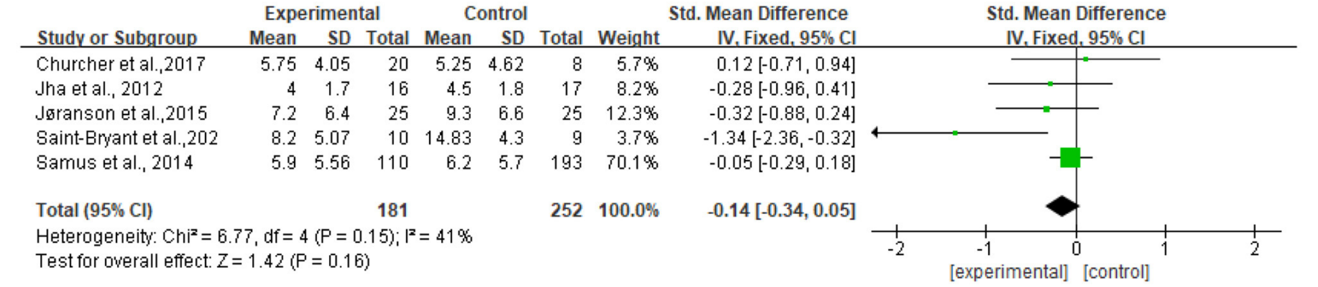


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.3.1 delete Ali et al., 2021								
Churcher et al.,2017	34	4.27	20	32.79	4.44	8	2.1%	0.27 [-0.55, 1.10]
Saint-Bryant et al.,202	33.6	6.17	10	30.78	5.65	9	1.7%	0.45 [-0.46, 1.37]
Samus et al., 2014	38.2	8.39	110	35.9	8.33	193	26.0%	0.27 [0.04, 0.51]
Surr et al., 2020	42.8	5.47	81	43.2	6.17	65	13.5%	-0.07 [-0.40, 0.26]
Waldorff et al.,2012	38.2	6.6	129	38.2	6.8	140	25.1%	0.00 [-0.24, 0.24]
Woods et al.,2012	36.63	5.63	206	35.96	5.28	144	31.6%	0.12 [-0.09, 0.33]
Subtotal (95% CI)			**556**			**559**	**100.0%**	**0.11 [-0.01, 0.23]**

Heterogeneity: Chi² = 4.55, df = 5 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.87 (P = 0.06)

Test for subgroup differences: Not applicable

FIGURE 5 | Sensitivity analyses of the intervention group vs. the control group on QOL-AD rating scores.



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Churcher et al.,2017	5.75	4.05	20	5.25	4.62	8	5.7%	0.12 [-0.71, 0.94]
Jha et al., 2012	4	1.7	16	4.5	1.8	17	8.2%	-0.28 [-0.96, 0.41]
Jøranson et al.,2015	7.2	6.4	25	9.3	6.6	25	12.3%	-0.32 [-0.88, 0.24]
Saint-Bryant et al.,202	8.2	5.07	10	14.83	4.3	9	3.7%	-1.34 [-2.36, -0.32]
Samus et al., 2014	5.9	5.56	110	6.2	5.7	193	70.1%	-0.05 [-0.29, 0.18]
Total (95% CI)			**181**			**252**	**100.0%**	**-0.14 [-0.34, 0.05]**

Heterogeneity: Chi² = 6.77, df = 4 (P = 0.15); I² = 41%
Test for overall effect: Z = 1.42 (P = 0.16)

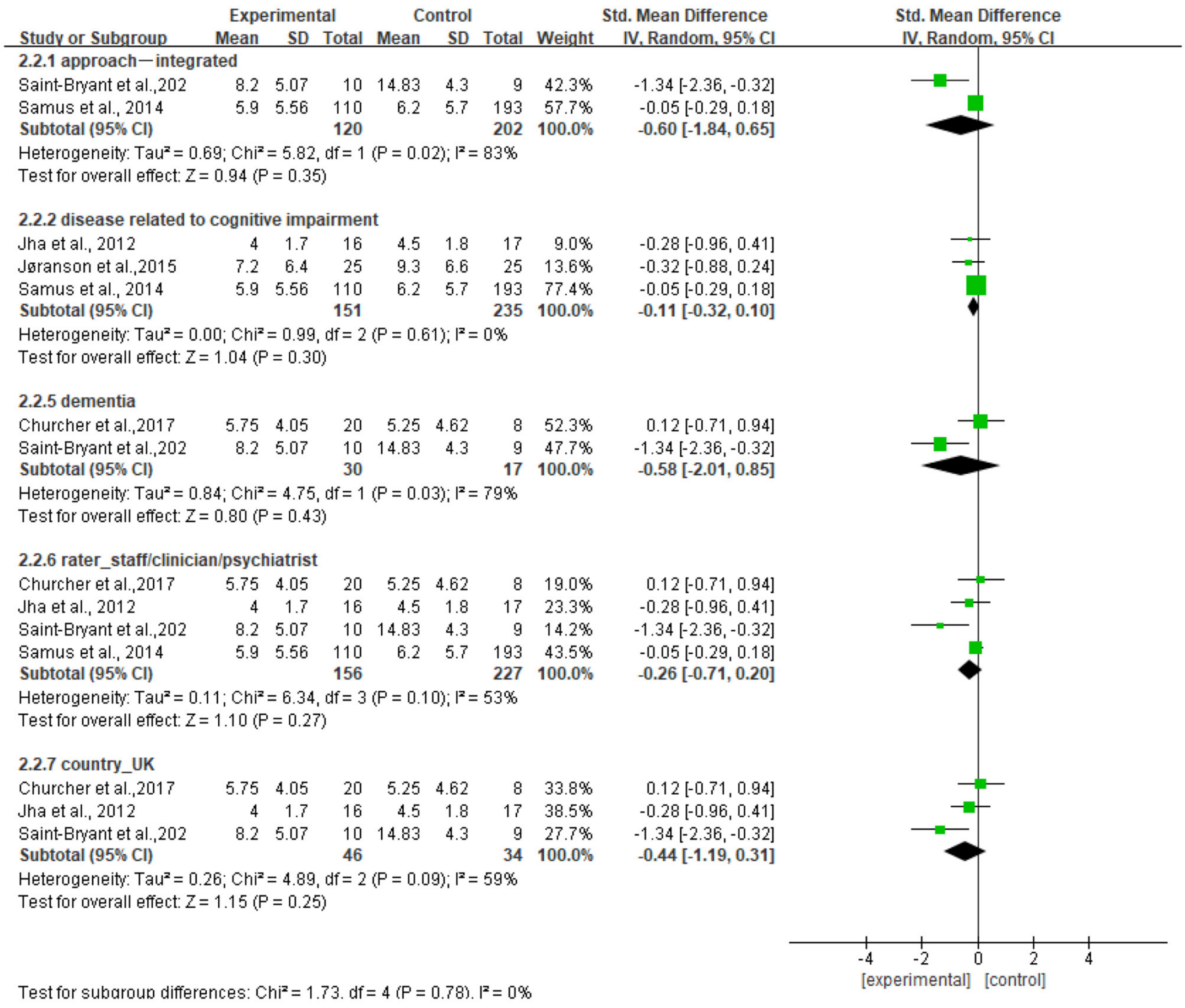
FIGURE 6 | Effect size of the intervention group vs. the control group on CSDD.

were inconclusive. However, the quality of RCTs included in our review is not very high. Only 5 of the 14 studies were judged low risk in allocation concealment, and only 3 of the 14 studies were judged low risk in blinding of participants and interventionists domains. Although it is very difficult to implement allocation concealment and blinding of participants and interventionists domains in real-world RCT research, it is strongly recommended that more rigorous RCT research should be carried out in the future, with special attention to allocation concealment and blinding of participants and interventionists domains.

In addition, our review identified integrated resilience approaches. In contrast, the reviews of Regan and Varanelli (33) focused on psychotherapeutic approaches; the review of Li et al. (31) paid more attention to resistance training, strength, and exercise programs; and the review of Carrion et al. (32) solely focused on cognitive therapy. A broader range of resilience approaches was considered in our review, which rendered interventions diverse. Among them, integrated resilience approaches that were used by most included studies involved multiple components, such as caregiver's support, social connection, and resource support. Results indicated the possible advantages of the multiple-component interventions and multidisciplinary teamwork in active coping with complex symptoms and stress of persons with neurocognitive disorders. Thus, we call for more resilience research using integrated approaches for persons with dementia to better understand the effectiveness of integrated approaches and how to appropriately adopt and implement them.

Furthermore, our review focused on psychosocial outcomes (e.g., QOL, ADL, mental health, coping ability, adaption, adjustment). However, social outcomes were measured less frequently. The meta-analysis of psychological outcomes was conducted, so it is impossible to judge the effect of resilience interventions on social outcomes, such as improving social connection, social well-being, and resource support. Similarly, Regan and Varanelli (33) assessed depression, anxiety, and adjustment. Carrion et al. (32) rated depression. In contrast, Li et al. (31) largely focused on the effect of resistance training on cognitive function, such as executive cognitive ability, global cognitive function, attention, and memory. Since there is no "gold standard" for measuring the outcomes of resilience interventions in persons with neurocognitive disorders, we recommend that the measurement instruments can be further developed and validated to measure more effectively.

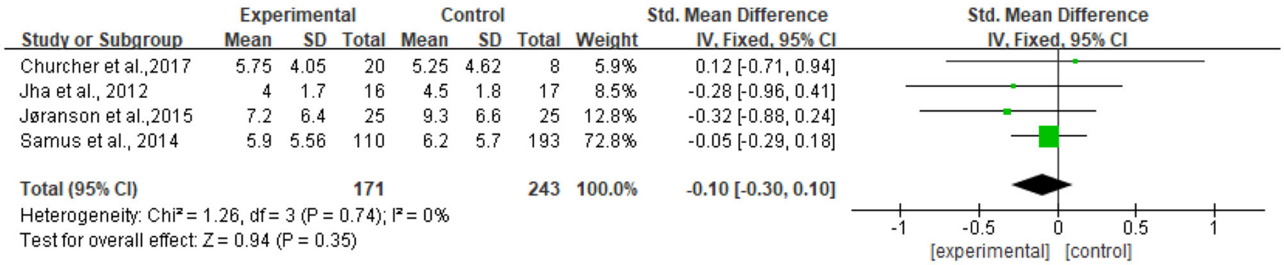
Additionally, regarding the effectiveness of resilience interventions, the previous systematic reviews' findings indicated positive effects (31, 33) or inconclusive (32) on different outcomes. However, due to the different design of the included original studies or the lack of meta-analysis of RCTs in these reviews, the statistical significance of the effect of resilience



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.2.1 approach—integrated								
Saint-Bryant et al.,202	8.2	5.07	10	14.83	4.3	9	42.3%	-1.34 [-2.36, -0.32]
Samus et al., 2014	5.9	5.56	110	6.2	5.7	193	57.7%	-0.05 [-0.29, 0.18]
Subtotal (95% CI)			**120**			**202**	**100.0%**	**-0.60 [-1.84, 0.65]**
Heterogeneity: Tau² = 0.69; Chi² = 5.82, df = 1 (P = 0.02); I² = 83%								
Test for overall effect: Z = 0.94 (P = 0.35)								
2.2.2 disease related to cognitive impairment								
Jha et al., 2012	4	1.7	16	4.5	1.8	17	9.0%	-0.28 [-0.96, 0.41]
Jøranson et al.,2015	7.2	6.4	25	9.3	6.6	25	13.6%	-0.32 [-0.88, 0.24]
Samus et al., 2014	5.9	5.56	110	6.2	5.7	193	77.4%	-0.05 [-0.29, 0.18]
Subtotal (95% CI)			**151**			**235**	**100.0%**	**-0.11 [-0.32, 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 2 (P = 0.61); I² = 0%								
Test for overall effect: Z = 1.04 (P = 0.30)								
2.2.5 dementia								
Churcher et al.,2017	5.75	4.05	20	5.25	4.62	8	52.3%	0.12 [-0.71, 0.94]
Saint-Bryant et al.,202	8.2	5.07	10	14.83	4.3	9	47.7%	-1.34 [-2.36, -0.32]
Subtotal (95% CI)			**30**			**17**	**100.0%**	**-0.58 [-2.01, 0.85]**
Heterogeneity: Tau² = 0.84; Chi² = 4.75, df = 1 (P = 0.03); I² = 79%								
Test for overall effect: Z = 0.80 (P = 0.43)								
2.2.6 rater_staff/clinician/psychiatrist								
Churcher et al.,2017	5.75	4.05	20	5.25	4.62	8	19.0%	0.12 [-0.71, 0.94]
Jha et al., 2012	4	1.7	16	4.5	1.8	17	23.3%	-0.28 [-0.96, 0.41]
Saint-Bryant et al.,202	8.2	5.07	10	14.83	4.3	9	14.2%	-1.34 [-2.36, -0.32]
Samus et al., 2014	5.9	5.56	110	6.2	5.7	193	43.5%	-0.05 [-0.29, 0.18]
Subtotal (95% CI)			**156**			**227**	**100.0%**	**-0.26 [-0.71, 0.20]**
Heterogeneity: Tau² = 0.11; Chi² = 6.34, df = 3 (P = 0.10); I² = 53%								
Test for overall effect: Z = 1.10 (P = 0.27)								
2.2.7 country_UK								
Churcher et al.,2017	5.75	4.05	20	5.25	4.62	8	33.8%	0.12 [-0.71, 0.94]
Jha et al., 2012	4	1.7	16	4.5	1.8	17	38.5%	-0.28 [-0.96, 0.41]
Saint-Bryant et al.,202	8.2	5.07	10	14.83	4.3	9	27.7%	-1.34 [-2.36, -0.32]
Subtotal (95% CI)			**46**			**34**	**100.0%**	**-0.44 [-1.19, 0.31]**
Heterogeneity: Tau² = 0.26; Chi² = 4.89, df = 2 (P = 0.09); I² = 59%								
Test for overall effect: Z = 1.15 (P = 0.25)								

Test for subgroup differences: Chi² = 1.73, df = 4 (P = 0.78), I² = 0%

FIGURE 7 | Subgroup analyses of the intervention group vs. the control group on CSDD.

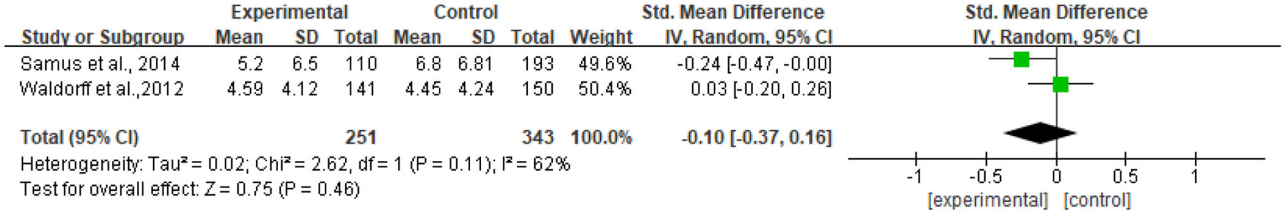


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Churcher et al.,2017	5.75	4.05	20	5.25	4.62	8	5.9%	0.12 [-0.71, 0.94]
Jha et al., 2012	4	1.7	16	4.5	1.8	17	8.5%	-0.28 [-0.96, 0.41]
Jøranson et al.,2015	7.2	6.4	25	9.3	6.6	25	12.8%	-0.32 [-0.88, 0.24]
Samus et al., 2014	5.9	5.56	110	6.2	5.7	193	72.8%	-0.05 [-0.29, 0.18]
Total (95% CI)			**171**			**243**	**100.0%**	**-0.10 [-0.30, 0.10]**

Heterogeneity: Chi² = 1.26, df = 3 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)

FIGURE 8 | Sensitivity analyses of the intervention group vs. the control group on CSDD rating scores.

interventions could not be judged, and the level of evidence was not high. Therefore, these conclusions of intervention effects needed to be drawn cautiously. One synthesis of systematic reviews also indicated that due to the heterogeneity of the included studies, there was no sufficient evidence to determine whether resilience interventions may promote psychosocial outcomes (48). Our meta-analysis of the RCTs confirmed that resilience interventions had significant benefit to persons with neurocognitive disorders in enhancing QOL but might not be beneficial in decreasing depression and neuropsychiatric



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Samus et al., 2014	5.2	6.5	110	6.8	6.81	193	49.6%	-0.24 [-0.47, -0.00]
Waldorff et al.,2012	4.59	4.12	141	4.45	4.24	150	50.4%	0.03 [-0.20, 0.26]
Total (95% CI)			**251**			**343**	**100.0%**	**-0.10 [-0.37, 0.16]**

Heterogeneity: Tau² = 0.02; Chi² = 2.62, df = 1 (P = 0.11); I² = 62%
Test for overall effect: Z = 0.75 (P = 0.46)

FIGURE 9 | Effect size of the intervention group vs. the control group on NPI-Q.

symptoms. It should be pointed out that several aspects of the original study limited the generalizability of our results: distinct approaches, diverse measurement tools and raters, and divergent settings and locations, and different data collection points during interventions and in f/u assessments. Therefore, further research is needed to address the development, implementation, and application of resilience interventions and conduct more rigorous and higher-quality RCT trials among persons with neurocognitive disorders.

This study has several limitations. First, due to the research team's language capacity, we only included English and Chinese literature, thus excluding potential useful information written in other languages. Second, although to some extent there was an accord on resilience as a dynamic process (14) and leading to psychosocial outcome (49, 50), and our review also identified various resilience interventions assessed by psychosocial outcomes, there was still no consensus about the definition of resilience and proper outcome measures. Thus, there may be some resilience studies that our study did not identify, and there could be other, equally valid, ways to define resilience that we did not consider. Last but not least, this study might be limited by the selected databases. Although the investigators included the most widely used English and Chinese databases, it remains possible that some works, particularly unpublished studies conducted in other countries, were not located and examined.

CONCLUSION

The study findings indicated significant benefits of resilience interventions on QOL but no significant benefits of resilience interventions on depression and neuropsychiatric behavioral symptoms among persons with neurocognitive disorders. There is an ongoing need for additional evidence to support the effectiveness of resilience interventions, how to further improve resilience interventions, how to implement them, and how to evaluate the effectiveness in persons with neurocognitive disorders. In addition, there is a need to strengthen methodological quality to assess and determine the effects of resilience interventions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YW led the conception, data extraction, risk bias assessment, data analysis, drafting, critical review, and revision of the manuscript. YZ and WC were responsible for data search, data screening, and extraction. TL helped to proofread and edit. IC critically revised the manuscript and eventually approved the upcoming version. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Hybrid Cognitive Behavioral Therapy With Interoceptive Exposure for Irritable Bowel Syndrome: A Feasibility Study

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Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder, which severely impairs the quality of life of patients. Treatment of refractory IBS patients is needed, but it is not yet widely available. Therefore, we previously developed a Japanese version of cognitive behavioral therapy with interoceptive exposure (CBT-IE) involving 10 face-to-face sessions to treat refractory IBS patients. To disseminate this treatment of IBS in places where therapists are limited, we further developed a hybrid CBT-IE program with complementary video materials that include psychoeducation and homework instructions so that patients can prepare for face-to-face sessions in advance at home and the session time can be shortened, thereby reducing the burden on both patient and therapist. In this study, we conducted a trial to evaluate the feasibility, efficacy, and safety of the hybrid CBT-IE program for Japanese IBS patients. The study was a single-arm, open-label pilot clinical trial. A total of 16 IBS patients were included in the study and 14 patients completed the intervention, which consisted of 10 weekly individual hybrid CBT-IE sessions. We performed an intention to treat analysis. The primary outcome measure for the efficacy of the intervention was a decrease in the severity of IBS symptoms. The feasibility and safety of the intervention were examined by the dropout rate and recording of adverse events, respectively. The dropout rate of the hybrid CBT-IE was comparable to that of our previous CBT-IE with only face-to-face sessions and no adverse events were recorded. The severity of IBS symptoms within-group was significantly decreased from the baseline to mid-treatment [Hedges' g = −0.98 (−1.54, −0.41)], post-treatment [Hedges' g = −1.48 (−2.09, −0.88)], 3-month follow-up

[Hedges' g = −1.78 (−2.41, −1.14)], and 6-month follow-up [Hedges' g = −1.76 (−2.39, −1.13)]. Our results suggest that the hybrid CBT-IE is effective and could be conducted safely. To confirm the effectiveness of the hybrid CBT-IE, it is necessary to conduct a multicenter, parallel-design randomized control trial.

Clinical Trial Registration: [https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000041376], identifier [UMIN000036327].

Keywords: feasibility study, complementary video materials, cognitive behavioral therapy with interoceptive exposure, irritable bowel syndrome, hybrid CBT

INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder of brain-gut interactions characterized by abdominal pain and bowel movement problems, such as diarrhea and constipation (1). Although IBS is not a fatal disease, patients' quality of life (QOL) can be significantly impaired (2, 3). Approximately 4.1% of the population worldwide are reported to be affected by IBS symptoms (4). The core pathophysiology of IBS is hypersensitivity to visceral stimulation involving increased autonomic arousal to visceral events (5, 6). Clinical and neurological studies have suggested that elevated central stress response enhances visceral sensitivity (7), which is similar to interoceptive hypersensitivity (8, 9). Gastrointestinal symptom-specific anxiety may play an important role in increasing pain sensitivity, hypervigilance, and poor coping behaviors (10, 11). As a result, visceral anxiety has been considered as the primary affective disturbance in IBS and as the mediator between other risk factors (e.g., neuroticism, trait anxiety, and worry) and IBS symptom severity (12). IBS symptoms can worsen with stressful situations or stimuli (13). These phenomena imply reciprocal brain-gut interactions as the mechanism between the symptoms of IBS and psychological processes (14).

Cognitive behavioral therapy (CBT) is applied not only to mental illness but also to refractory IBS. In the clinical guidelines for IBS proposed by the Japanese Society of Gastroenterology, the treatment of IBS consists of three stages (15, 16). If the patients' condition does not improve in the first stage (e.g., diet, life-style guidance, and pharmacotherapies for gastrointestinal symptoms), the second stage (e.g., psychotropic drug therapy) is applied. Finally, psychotherapy (e.g., CBT, hypnotherapy, and relaxation methods) is used as the third stage of intervention for refractory IBS (17)[1]. Among the various types of CBT protocols, CBT using interoceptive exposure (CBT-IE) to visceral sensations is one of the most promising psychotherapies for IBS. Interoceptive exposure (IE) focuses on reducing anxiety and avoidance response to visceral sensations. IE weakens the fear response by enabling new learning that competes with the initial fearful associations (18). CBT-IE consists of two components. The first is similar to traditional CBT and includes education about IBS symptoms that reflect conditional reactions to reminders of gastrointestinal distress, self-monitoring of IBS symptoms, attention control training to learn to shift focus away rather than perseverate unpleasant visceral sensations (19), cognitive therapy to identify and challenge threat-laden appraisals of visceral sensations, and *in-vivo* exposure to feared/avoided situations. The second component is IE with repeated exposure to visceral sensations, such as tightening the abdomen to produce gut sensations, delaying defecation, and eating feared/avoided foods. IE is expected to reduce fear of sensations, as the procedure is aimed at alleviating gastrointestinal symptom-specific anxiety by purposely evoking bodily sensations that IBS patients fear (18). Craske et al. examined the efficacy of CBT-IE protocol compared to stress management (SM) or attention control (AC). They reported that CBT-IE outperformed AC on several indexes of outcome, and outperformed SM in some domains. Incidentally, no differences were observed between SM and AC. The results suggest that CBT-IE may be a particularly effective treatment for IBS (18).

Therefore, we developed a Japanese version of CBT-IE involving 10 face-to-face sessions including the same contents as the original CBT-IE for IBS (18). Our feasibility study of the Japanese version of CBT-IE showed a significant reduction of IBS symptoms and a remarkable improvement in IBS-specific QOL post-intervention, at the 3-month and 6-month follow-ups, compared with the pre-intervention state (20). Originally, the Japanese version of face-to-face CBT-IE (20) consisted of 10 × 60-min sessions. We realized that this structure was burdensome for patients and therapists and disadvantageous for widespread use in the current situation where the number of therapists is limited, and this led us to develop a hybrid CBT-IE. To overcome the difficulties in disseminating this intervention widely to clinical settings in Japan, due to a shortage of cognitive behavioral therapists and the highly time-consuming process of CBT (20), we further developed a hybrid CBT-IE program. This comprised complementary video materials, including psychoeducation and homework instructions, to allow patients to prepare at home before each face-to-face session. Consequently, the length of the face-to-face sessions was shortened from 60 to 30 min.

In this study, we conducted a trial to evaluate the feasibility, efficacy, and safety of the hybrid CBT-IE program for Japanese IBS patients. The efficacy of the intervention was measured by whether a significant reduction of IBS symptoms was reported post-treatment during follow-ups compared with the pre-intervention. Feasibility and safety were

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Abbreviations: IBS, irritable bowel syndrome; CBT, cognitive behavioral therapy; CBT-IE, cognitive behavioral therapy using interoceptive exposure; AC, attention control; QOL, quality of life; M.I.N.I., Mini-International Neuropsychiatric Interview; LMM, linear mixed model; RCT, randomized control trial.

[1] https://www.ncbi.nlm.nih.gov/pubmed/21656972

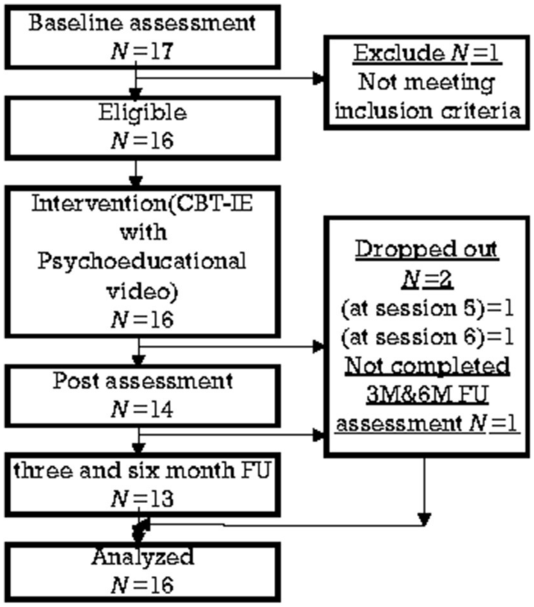

FIGURE 1 | Diagram.

evaluated by the dropout rate and incidence of severe adverse events, respectively.

We hypothesized that severity of IBS, abdominal anxiety, IBS-related QOL and health-related QOL would improve at the end of the hybrid CBT-IE as well as at follow-ups compared with the baseline.

METHODS

Study Design

This study was a single-arm, open-label trial. The trial was registered as a feasibility study and conducted at the National Center of Neurology and Psychiatry (NCNP) Hospital in Kodaira, Japan.

Participants and Recruitment

Participants were recruited from an IBS-specialized outpatient unit of the NCNP Hospital; they were referred by their primary physicians or voluntarily contacted the researchers in response to an advertisement on the NCNP homepage.

The flow of participants is shown in **Figure 1**. Participants were included if they (i) were diagnosed by physicians (TA, YT, and HA) as suffering IBS according to the Rome III criteria (21); (ii) were at least 16 years old at the time of screening assessment; (iii) showed ≥175 points (i.e., moderate severity) on the Irritable Bowel Syndrome Severity Index (IBSSI-J) during screening assessment; and (iv) were able to understand the purpose of this study and its contents, and provide written informed consent. Participants could withdraw at any time without penalty. The Mini-International Neuropsychiatric Interview (M.I.N.I.) was also conducted as screening by physicians (TA or YT). The subjects were assessed through interviews with the researchers, two psychosomatic physicians, and the subjects were included in the study. The exclusion criteria are shown in **Table 1**.

TABLE 1 | Eligibility criteria and warning symptoms list.

1. Person in whom organic disease is suggested by the presence of warning symptoms*.
2. Persons with a history of or concomitant inflammatory bowel disease, malignant tumor, or other bowel disease which could cause the current bowel symptoms.
3. Persons suffering from major psychiatric disease, such as psychotic disorders, bipolar disorder, substance abuse-related disorders, or eating disorders (persons with anxiety disorders and depression without suicidal ideation are not excluded)
4. Persons with antisocial personality disorders.
5. Persons observed to have significant suicidal ideation at screening.
6. Persons with another past or present psychiatric or physical disease that is likely to interfere with continuation and evaluation of the study.
7. Persons experiencing any other type of marked chronic pain.
8 . Those taking narcotic analgesics.
9. Persons who anticipate difficulty attending 10 sessions as an outpatient during the 16-week CBT implementation period.
10. Those who have previously received structured individual CBT.
11. Those for whom verbal and written communication in Japanese is not possible.
12. Pregnant or lactating women.
13. Any other person whom the principal investigator has determined to be unsuitable as a participant of the study.

*Warning symptoms list.

1. Symptoms which first appeared after 50 years of age.
2. Any rectal bleeding that has not undergone sufficient medical investigation (excluding that caused by known hemorrhoids).
3. Diarrhea-predominant IBS in which no colonoscopy investigation has been conducted.
4. Unexplained weight loss without a change in eating habits.
5. Nocturnal symptoms sufficient to cause insomnia.
6. The presence of warning symptoms (anemia, inflammatory reactions, or fecal occult blood).
7. Persons with a family history of colon cancer in a first- or second-degree relative (grandparents, parents, siblings, or children).

https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000041376.

Sample Size

We determined a target sample size of 20 participants considering dropout rates (15%) estimated based on our previous face-to-face feasibility study of CBT-IE for IBS (20) and the recommendation that more than 12 participants are suitable for pilot studies (22).

Study Procedures

After the screening, the hybrid CBT-IE interventions were conducted at the outpatient service in the NCNP Hospital for eligible IBS participants. Participants completed a baseline assessment before the first session, a mid-treatment assessment when they finished their fifth session of CBT-IE, and a post-treatment assessment when all sessions were completed. At 3 and again at 6 months after completion of the intervention, a follow-up assessment was performed.

TABLE 2 | Contents of each session (23).

Session number	Contents of intervention	Handouts	Play time of Video
1	Education about IBS and psychological stress on digestive functioning, awareness-raising	• Personal IBS profile (in session use) • Monitoring IBS distress	(12′ 16″)
2	Education about the role of conditioning in IBS, attentional training	• Monitoring IBS distress • Guide for Attentional training • Common IBS symptom appraisal list	(6′ 44″)
3	Attentional training, cognitive restructuring for IBS sensations and risk estimates	• Monitoring IBS distress • Common IBS symptom appraisal list	(9′ 31″)
4	Cognitive restructuring for symptoms of IBS, valence estimates, hierarchy construction for IBS sensation reminders	• Monitoring IBS distress • Deliberate exposure hierarchy	(9′ 05″)
5	Cognitive restructuring, interoceptive exposure assessment, *in vivo* exposure	• Monitoring IBS distress • Interoceptive exposure exercises • Interoceptive exposure FAQ • Guide for IBS and *in-vivo* exposure • *In vivo* exposure instructions • Deliberate exposure record	(11′ 36″)
6–9	Conduct of Interoceptive exposure, *in vivo* exposure	• Monitoring IBS distress • Interoceptive exposure instructions • Interoceptive exposure record	(5′ 40″) (3′ 32″) (3′ 43″) (3′ 35″)
10	Interoceptive exposure, *in vivo* exposure, summary of the all sessions, relapse prevention	• Monitoring IBS distress • Relapse prevention Map • Dealing with setbacks • List of positive Accomplishments	(7′ 44″)

Hybrid CBT-IE for IBS

We developed a hybrid CBT-IE protocol for this study consisting of face-to-face sessions and self-study using psychoeducational videos based on Craske et al.'s original CBT-IE (18). We did not change the contents of the original protocol, except for making a textbook and psychoeducational video materials for patients. The textbook contents included pictures, illustrations, and figures to aid patients' understanding. It also contained homework worksheets for self-monitoring. The video materials consisted of 10 lectures about IBS mechanisms and behavioral-cognitive skills. CBT-IE consisted of the following seven components: (1) psychoeducation about IBS symptoms, including the mechanism by which symptoms are maintained; (2) self-monitoring and development of the CBT model of IBS; (3) learning AC skills for modifying attention bias to visceral sensations; AC (19) is training that teaches patients to shift the focus of unpleasant visceral sensations, rather than tolerate them. In this program, multiple sounds, such as a metronome and noise, are presented simultaneously, and voice guidance is used to practice paying attention to and switching between each sound; (4) cognitive restructuring for the anxiety related to IBS symptoms and visceral sensations; (5) *in-vivo* exposure to situations that each patient feared or avoided because of anxiety about the occurrence of IBS symptoms (which was personalized considering each participant's tolerance); (6) IE to abdominal sensations that patients feared, for example, by tightening a belt on patients' midriff or drinking something cold; and (7) relapse prevention (see **Table 2**, **Figure 2**).

Patients were offered 10 face-to-face session of 30 min each combined with pre-learning of video material (**Figure 2**). One course was performed within 4 months. Before the face-to-face session began, we gave the subjects the printed material and YouTube URL for the first session. At the end of each session, we gave the subjects both the YouTube URL and video material for the next session. Participants were instructed to recognize IBS symptoms and apply cognitive behavioral skills through the video as homework before each session. Patients' understanding of the contents of the video and text, and their practice of homework was reviewed in the subsequent face-to-face session.

Therapists

The hybrid CBT-IE interventions were conducted by two clinical psychologists (HitK and MF) with clinical experience in a psychiatric setting of 7 and 18 years, respectively. Interventions were supervised by the third author (YF), who is a licensed clinical psychologist, and the last author (TA), who is a specialist in psychosomatic medicine. Medical treatments and management were performed by two physicians who are specialists in psychosomatic medicine (TA and YT).

Quality Assurance

Therapists used a therapeutic manual of CBT-IE to practice all seven components. They also received regular training on hybrid CBT-IE by supervisors (TA and YF) to maintain treatment fidelity. All the hybrid CBT-IE sessions were subject to evaluations of treatment adherence using treatment manuals.

Homework Adherence

Therapists asked participants certain questions to check for homework adherence. Examples of questions are as follows: "Did

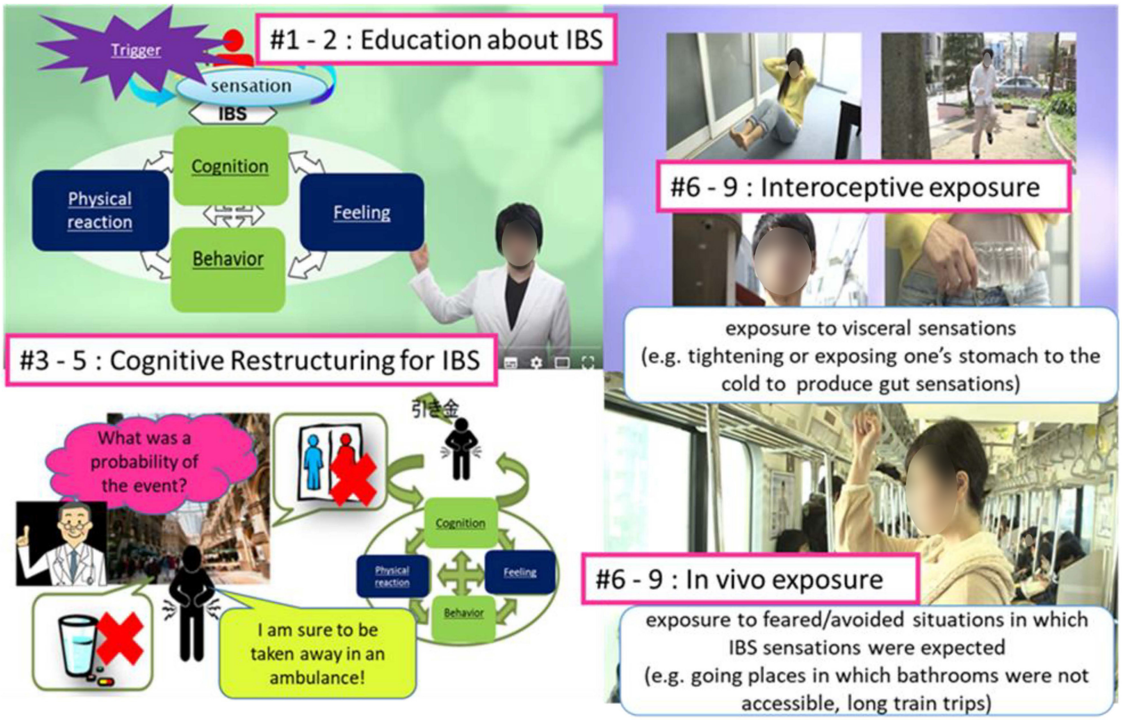

FIGURE 2 | Contents of psychoeducational videos.

you watch the video before the session?" "Please explain what you understand about the video," and "Are there any questions about this session?" When participants asked questions about the session, the therapist provided details or gave tips about doing homework. If a participant did not do the homework, the therapist explained the session's content and worked on the homework with the participant.

Safety Monitoring

In this study, subjects were asked to report adverse events at every CBT session and physician visit. Each participant received checkups every 2 weeks or once a month and adverse events were examined by physicians (TA and YT) throughout the intervention period. The therapists also monitored severe adverse events at every CBT-IE session from participants' verbal reports.

Medication

Each participant's unique medication was kept constant or could be reduced, but neither increased doses or new doses were allowed throughout the research period.

Measures

Primary Outcome Measure: IBS Severity Index

The Japanese version of the IBS Severity Index (IBSSI-J, which is the same as the Japanese version of the IBS Symptoms Severity Scale, IBS-SSS) evaluates the severity of IBS symptoms and is a valid and reliable assessment tool for Japanese patients (24, 25). This self-reported instrument has items that score abdominal pain, abdominal distention, bowel movements, and QOL. The total score ranges from 0 to 500. Severity is graded as mild (75–174), moderate (175–299), or severe (300–500).

Secondary Outcome Measures

Gastrointestinal Symptom-Specific Anxiety (Visceral Sensitivity Index)

The Visceral Sensitivity Index (VSI) scale evaluates gastrointestinal symptom-specific anxiety (10, 26). The scale includes 15 items scored on a 6-point Likert scale. Lower scores indicate greater severity of anxiety about abdominal symptoms.

Disease-Specific Quality of Life for IBS

The disease-specific quality of life for IBS (IBS-QOL) measure was used to assess IBS-specific QOL (27). This 34-item 5-point Likert scale examines how IBS affects the daily functioning of a participant. The scale includes eight subscales: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual concerns, and relationships. A higher total score of subscales combined indicates better QOL.

Health-Related QOL (36-Item Short-Form Health Survey)

The health-related QOL was assessed using the short-form health survey (SF-36) (28). This 36-item scale consists of eight subscales: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. A higher total score indicates better health related QOL.

Anxiety (State-Trait Anxiety Inventory)

Anxiety was assessed using the State-Trait Anxiety Inventory (STAI) (29). This 40-item scale, answered using 4-point Likert scales, assesses both trait and state anxiety. A higher total score indicates the presence of higher intensity anxiety.

Depression (Beck Depression Inventory-II)

Depression was assessed using the Beck Depression Inventory-II (BDI-II) (30, 31). This 21-item scale utilizes a 4-point Likert scale, and a higher total score indicates the presence of higher severity depression.

Irritable Bowel Syndrome Global Improvement Scale

In the IBS Global Improvement Scale (IBS-GIS), patients assess improvement of IBS using a 7-point Likert scale (32). Participants completed a questionnaire mid-treatment, post-treatment, and at the 3-month and 6-month follow-ups by recording a rating of IBS global improvement ("Compared to the way you usually felt during the 3 months before you entered the study, have your IBS symptoms over the past 4 weeks been substantially worse = 7, moderately worse = 6, slightly worse = 5, unchanged = 4, slightly improved = 3, moderately improved = 2, or substantially improved = 1?"). In line with previous research (32), we defined people with a score less than 3 (with 1 or 2) on the IBS-GIS as treatment responders in this study.

Ethical Approval

Prior to the start of this study, participants provided written informed consent. This study received approval from the ethical review board of the NCNP (approval number: A2015-118). The study was also registered to a clinical trials registry (UMIN000036327; https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000041376).

Data Analysis

We calculated the dropout rate to evaluate the feasibility of the hybrid CBT-IE for IBS. In addition, we estimated the change in all outcome variables over time based on a linear mixed model (LMM) considering missing values due to dropouts with SPSS version 26 (SPSS Inc) with intention to treat. In this analysis, each assessment period was included as a categorical fixed effect and participants were included as a random effect. The LMM can be applied to test the difference of means between conditions for data that have been measured repeatedly under several conditions. In the LMM analysis, the assessment period (level: pre-assessments, mid-assessments, and post-assessments) was included as the categorical fixed effect and participants were included as a random effect. Then we estimated treatment effect for each assessment period based on parameter estimates of fixed effects. Thus, we reduced the bias caused by missing values due to dropout, compared to the case where only the data at each time point are used for estimation. In addition, Hedges' g showed a 95% confidence interval from the LMM for each treatment visit (pre-mid treatment, pre-post treatment, pre-3 month follow up, pre-6 month follow up, post-3 month follow up, and post-6 month follow up) within-group was calculated to examine the impact of the hybrid CBT-IE's efficacy using an effect size calculator (https://www.cem.org/effect-size-calculator).

TABLE 3 | Demographic data.

Demographic variables	Value
Gender	
Women, *N* (%)	12 (71)
Age (years), mean (*SD*)	36.76 (13.41)
Median	35
Range	17–65
Duration of IBS (years), mean (*SD*)	14.12 (11.66)
Median	9
Range	2–45
Type of IBS, *N* (%)	
IBS-D	13 (76)
IBS-C	1 (6)
IBS-M	0 (0)
IBS-U	3 (18)
Employment status, *N* (%)	
Employed full-time	7 (41)
Employed full-time, suspended from work	1 (6)
Employed part-time	1 (6)
Unemployed	8 (47)
Marital status, *N* (%)	
Single	7 (41)
Married	9 (53)
Divorce/Widow	1 (6)
Educational background, *N* (%)	
High school student	1 (6)
High school	2 (12)
≧2 years of college/university	14 (82)

As a supplementary analysis, we compared the dropout and responder rates at post-treatment and follow-ups using 50% or greater improvement on the IBSSI-J from the baseline and VSI, the IBS-GIS as defined in the GIS section of the face-to-face only CBT-IE, and the hybrid CBT-IE feasibility study using the chi-square test.

RESULTS

Characteristics of Participants

The recruitment of participants began in October 2016 and the last 6-month follow-up assessment ended in November 2019. **Table 3** indicates the characteristics of participants. A total of 17 participants were screened and 16 of them were eligible. One participant was ruled out by a doctor because a comorbid olfactory reference syndrome, which was thought to interfere with the implementation of CBT-IE, was identified after screening. Two participants dropped out before they completed the intervention. One participant lost motivation before the fifth session. Another dropped out before the sixth session, getting depressed by the ongoing distress of a long-standing family conflict.

The median IBS duration of participants included this study was 9 years (range of 2–45 years). The percentage of IBS types

TABLE 4 | Descriptive statistics of outcome measures (mean and standardized deviation).

	Pre		Mid		Post		3 months follow up		6 months follow up	
	Mean	***SD***	**Mean**	***SD***	**Mean**	***SD***	**Mean**	***SD***	**Mean**	***SD***
IBSSI-J	294.06	75.79	206.43	71.88	165.00	88.90	137.88	77.51	139.23	82.26
VSI	19.94	14.18	30.21	13.74	37.79	12.22	41.15	16.12	41.08	18.63
IBS-QOL										
Tolal	52.63	18.87	70.29	19.06	81.00	9.49	82.00	11.30	80.69	12.87
Dysphoria	38.50	22.00	59.57	27.65	75.71	16.34	80.31	10.87	77.38	16.90
Interference with activity	38.44	21.81	56.00	24.27	70.00	13.50	71.69	16.22	72.38	16.16
Body image	75.94	22.52	85.43	19.54	89.43	10.78	88.08	15.80	88.08	12.26
Health worry	50.94	25.55	81.57	22.13	86.36	16.60	86.00	14.62	82.69	16.87
Food avoidance	43.19	37.28	67.79	28.82	84.50	15.27	81.46	21.53	79.46	18.73
Social reaction	74.00	18.45	83.57	16.78	91.21	9.67	88.62	13.27	88.62	12.65
Sexual concerns	86.00	18.71	93.79	16.00	96.43	9.08	94.62	9.49	95.31	10.69
Relationships	53.56	20.84	70.93	18.47	76.71	15.72	80.38	12.65	78.92	18.26
SF-36										
Physical functioning	49.75	15.11	54.50	5.83	53.93	5.57	56.00	2.80	59.54	11.70
Physical role	46.06	10.58	48.21	9.64	49.79	7.90	51.00	5.29	56.31	12.98
Bodily pain	44.19	13.47	44.00	14.67	49.79	9.79	50.31	9.12	53.54	13.63
General health	40.81	12.83	42.29	9.38	48.50	12.13	47.92	12.18	48.92	19.01
Vitality	44.06	11.19	47.29	7.19	48.29	9.84	46.23	11.94	50.25	19.82
Social functioning	46.94	14.83	47.79	11.54	53.36	7.86	51.62	6.85	52.58	17.14
Emotional role	44.69	10.58	50.36	7.83	50.71	8.05	52.23	5.95	55.08	14.34
Mental health	44.06	9.15	47.86	6.87	50.79	7.23	49.00	7.89	51.83	15.47
STAI										
Trait anxiety	53.69	10.22	49.36	9.06	45.86	10.06	46.46	11.38	45.15	12.19
State anxiety	47.31	11.25	39.93	10.82	38.00	8.68	38.77	10.93	37.85	9.86
BDI-II										
Total	12.31	6.71	8.29	7.47	6.57	5.50	6.85	7.29	6.85	6.41

IBSSI, Irritable Bowel Syndrome Severity Index; VSI, Vischeral Sensitivity Index; IBS-QOL, Irritable Bowel Syndrome-Quality Of Life; SF-36, MOS 36-Item Short-Form Health Survey; STAI, State-Trait Anxiety Inventory; BDI-II, Beck Depression Inventory-II.

were: IBS with diarrhea (IBS-D) = 76%, IBS with constipation (IBS-C) = 6%, mixed IBS (IBS-M) = 0%, and unclassified IBS (IBS-U) = 18%.

Comorbidities

One participant had comorbid panic disorder with agoraphobia and social anxiety disorder (6%), another participant had comorbid agoraphobia and general anxiety disorder (6%), and three participants had comorbid agoraphobia (18%) based on the M.I.N.I (**Table 3**).

Dropout Rates

The dropout rate in this study was 12.5% ($N = 2/16$), which is similar to the dropout rate of our previous feasibility study of CBT-IE for IBS with face-to-face sessions (15%, $N = 3/20$) (20). A chi-square test showed no statistically significant differences between the two.

Primary Outcome Measures

Table 4 shows the mean and standard deviation of the primary and secondary outcome measures at baseline, mid-treatment, post-treatment, and 3- and 6-month follow-up assessments. **Table 5** shows estimated mean differences (MD) and standardized mean differences (Hedges' g) of the outcome measures with a 95% confidence interval. The *post-hoc* power for the primary endpoint at post treatment visit was estimated as >99%.

The IBSSI-J improved significantly from baseline to mid-treatment, post-treatment, 3-month follow-up, and 6-month follow-up. The effect size of the IBSSI-J was large from baseline to mid-treatment [Hedges' g = −0.98 (−1.54, −0.41)], post-treatment [Hedges' g = −1.48 (−2.09, −0.88)], 3-month follow-up [Hedges' g = −1.78 (−2.41, −1.14)], and 6-month follow-up [Hedges' g = −1.76 (−2.39, −1.13)].

Secondary Outcome Measures

The VSI improved significantly from baseline to post-treatment, 3-month follow-up, and 6-month follow-up. The effect size of the VSI was large from baseline to post-treatment [Hedges' g = 1.06 (0.49, 1.63)], from baseline to 3-month follow-up [Hedges'

TABLE 5 | Estimated mean difference and standardized mean difference with 95% confidence interval LMM.

	Baseline to mid-treatment		Baseline to post-treatment		Baseline to 3 months follow up		Baseline to 6 months follow up		Post-treatment to 3 months follow up		Post-treatment to 6 months follow up	
	MD (95%CI)	**SMD (Hedges'g, 95%CI)**	**MD (95%CI)**	**SMD (Hedges'g, 95%CI)**	**MD (95%CI) (Hedges'g, 95%CI)**	**SMD**	**MD (95%CI) (Hedges'g, 95%CI)**	**SMD (Hedges'g, 95%CI)**	**MD (95%CI)**	**SMD (Hedges'g, 95%CI)**	**MD (95%CI)**	**SMD**
IBSSI-J total	**−79.80**	**−0.98**	**−121.22**	**−1.48**	**−144.96**	**−1.78**	**−143.61**	**−1.76**	−23.73	−0.29	−22.34	−0.27
(primary measure)	**[−132.18, −27.40]**	**[−1.54, −0.41]**	**[−173.61, −68.84]**	**[−2.09, −0.88]**	**[−198.63, −91.28]**	**[−2.41, −1.14]**	**[−197.28, −89.94]**	**[−2.39, −1.13]**	[−85.50, 38.04]	[−0.84, 0.26]	[−84.15, 39.38]	[−0.82, 0.27]
VSI total	**8.79 [0.99, 16.60]**	**0.57 [0.02, 1.12]**	**16.36 [8.56, 24.17]**	**1.06 [0.49, 1.63]**	**18.51 [10.51,26.51]**	**1.20 [0.62, 1.78]**	**18.43 [10.43, 26.43]**	**1.19 [0.61, 1.78]**	2.14 [−7.01, 11.30]	0.14 [−0.40, 0.68]	2.07 [−7.09, 11.22]	0.13 [−0.41, 0.68]
IBS-QOL												
Tolal	**16.05 [6.78, 25.33]**	**1.04 [0.46, 1.61]**	**26.77 [17.49, 36.05]**	**1.73 [1.1, 2.36]**	**27.15 [6.78, 25.33]**	**1.75 [1.12, 2.38]**	**25.84 [16.33, 35.35]**	**1.67 [1.05, 2.29]**	0.38 [−10.54, 11.30]	0.02 [−0.52, 0.57]	−0.93 [−11.85, 9.99]	−0.06 [−0.60, 0.48]
Dysphoria	**19.75 [6.16, 33.34]**	**0.96 [0.40, 1.53]**	**35.90 [22.31, 49.49]**	**1.75 [1.12, 2.38]**	**38.57 [24.65, 52.50]**	**1.88 [1.24, 2.52]**	**35.65 [21.73, 49.57]**	**1.74 [1.11, 2.36]**	2.68 [−13.40, 18.72]	0.13 [−0.41, 0.68]	−0.25 [−16.28, 15.79]	−0.01 [−0.56, 0.53]
Interference with activity	**16.07 [4.68, 27.46]**	**0.83 [0.27, 1.39]**	**30.07 [18.68, 41.46]**	**1.55 [0.95, 2.16]**	**30.66 [18.99, 42.34]**	**1.59 [0.97, 2.20]**	**31.35 [19.68, 43.02]**	**1.62 [1.01, 2.24]**	0.59 [−12.81, 14.68]	0.03 [−0.51, 0.57]	1.28 [−12.12, 14.68]	0.07 [−0.48, 0.61]
Body image	8.03 [−0.31, 16.38]	0.45 [−0.09, 0.99]	**12.03 [3.69, 20.38]**	**0.68 [0.12, 1.23]**	**11.78 [3.22, 20.33]**	**0.66 [0.11, 1.21]**	**11.78 [3.22, 20.33]**	**0.66 [0.11, 1.21]**	−0.26 [−10.03, 9.52]	−0.01 [−0.56, 0.53]	−0.26 [−10.03, 9.52]	−0.01 [−0.56, 0.53]
Health worry	**29.79 [18.28, 41.30]**	**1.50 [0.90, 2.10]**	**34.57 [23.06, 46.08]**	**1.74 [1.12, 2.37]**	**33.59 [21.79, 45.39]**	**1.69 [1.08, 2.31]**	**30.28 [18.49, 42.08]**	**1.53 [0.92, 2.13]**	−0.98 [−14.52, 12.55]	−0.05 [−0.59, 0.49]	−4.29 [−17.82, 9.24]	−0.22 [−0.76, 0.32]
Food avoidance	**21.17 [4.96, 37.38]**	**0.77 [0.21, 1.33]**	**37.88 [21.67, 54.09]**	**1.39 [0.78, 1.99]**	**33.93 [17.32, 50.54]**	**1.24 [0.65, 1.83]**	**31.93 [15.32, 48.54]**	**1.17 [0.58, 1.75]**	−3.95 [−23.03, 15.12]	−0.14 [−0.69, 0.40]	−5.91 [−25.03, 13.12]	−0.22 [−0.77, 0.33]
Social reaction	**8.43 [0.53, 16.32]**	**0.56 [0.01, 1.11]**	**16.07 [8.18, 23.97]**	**1.07 [0.50, 1.64]**	**14.04 [5.95, 22.14]**	**0.94 [0.37, 1.50]**	**14.04 [5.95, 22.14]**	**0.94 [0.37, 1.50]**	−2.03 [−11.29, 7.24]	−0.13 [−0.68, 0.41]	−2.03 [−11.29, 7.24]	−0.13 [−0.68, 0.41]
Sexual concerns	5.69 [−4.23, 15.60]	0.39 [−0.18, 0.95]	8.33[−1.58, 18.24]	**0.57 [0.00, 1.13]**	6.89 [−3.26, 17.05]	0.47 [−0.10, 1.03]	7.58 [−2.57, 17.74]	0.51 [−0.05, 1.08]	−1.44 [−13.16, 10.28]	−0.10 [−0.67, 0.47]	−0.75 [−12.47, 10.98]	−0.05 [−0.62, 0.52]
Relationships	**15.72 [4.44, 27.00]**	**0.88 [0.32, 1.44]**	**21.50 [10.22, 32.79]**	**1.20 [0.62, 1.78]**	**25.42 [13.86, 36.97]**	**1.42 [0.82, 2.02]**	**23.95 [12.40, 35.51]**	**1.34 [0.75, 1.93]**	3.91 [−9.38, 17.20]	0.22 [−0.33, 0.76]	2.45 [−10.84, 15.74]	0.14 [−0.41, 0.68]
SF-36												
Physical functioning	2.56 [−3.62, 8.73]	0.20 [−0.37, 0.77]	1.98 [−4.19, 8.16]	0.16 [−0.41, 0.72]	4.26 [−2.07, 10.59]	0.34 [−0.23, 0.91]	**7.80 [1.47, 14.12]**	**0.62 [0.04, 1.20]**	2.28 [−4.97, 9.52]	0.18 [−0.40, 0.76]	5.81 [−1.43, 13.06]	0.46 [−0.12, 1.04]
Role physical	1.90 [−6.09, 9.89]	**0.81 [0.25, 1.36]**	3.47 [−4.52, 11.47]	**0.97 [0.41, 1.53]**	4.71 [−3.47, 12.89]	**1.09 [0.53, 1.66]**	**10.02 [1.84, 18.20]**	**1.63 [1.02, 2.25]**	1.24 [−8.26, 10.74]	0.13 [−0.41, 0.67]	6.55 [−2.95, 16.04]	**0.67 [0.11, 1.22]**
Bodily pain	−0.84 [−11.21, 9.53]	−0.07 [−0.61, 0.47]	4.95 [−5.42, 15.32]	0.39 [−0.15, 0.93]	5.70 [−4.90, 16.31]	0.45 [−0.09, 0.99]	8.93 [−1.67, 19.54]	**0.70 [0.15, 1.26]**	0.75 [−11.57, 13.78]	0.06 [−0.49, 0.61]	3.98 [−8.34, 16.31]	0.31 [−0.24, 0.87]
General health	0.83 [−7.91, 9.56]	0.06 [−0.47, 0.59]	7.04 [−1.70, 15.78]	0.52 [−0.02, 1.06]	5.75 [−3.20, 14.70]	0.42 [−0.12, 0.96]	6.75 [−2.20, 15.70]	0.50 [−0.04, 1.04]	−1.29 [−11.59, 9.01]	−0.09 [−0.64, 0.45]	−0.29 [−10.59, 10.01]	−0.02 [−0.56, 0.52]
Vitality	2.77 [−5.06, 10.59]	−0.03 [−0.58, 0.51]	3.77 [−4.06, 11.59]	0.40 [−0.15, 0.95]	1.31 [−6.71, 9.33]	0.20 [−0.35, 0.75]	5.29 [−2.94, 13.52]	0.22 [−0.32, 0.77]	−2.46 [−11.67, 6.76]	−0.19 [−0.74, 0.36]	1.53 [−7.93, 10.98]	0.12 [−0.43, 0.67]
Social functioning	−0.41 [−9.35, 8.52]	−0.03 [−0.58, 0.52]	5.16 [−3.78, 14.09]	0.40 [−0.16, 0.96]	2.60 [−6.55, 11.75]	0.20 [−0.35, 0.75]	3.41 [−5.98, 12.80]	0.26 [−0.29, 0.82]	−2.56 [−13.12, 8.01]	−0.20 [−0.76, 0.37]	−1.75 [−12.58, 9.09]	−0.14 [−0.70, 0.43]
Role emotional	5.63 [−1.66, 12.92]	**0.57 [0.04, 1.11]**	5.99 [−1.30, 13.28]	**0.61 [0.07, 1.15]**	**7.53 [0.06, 14.99]**	**0.77 [0.23, 1.31]**	**10.37 [2.91, 17.83]**	**1.06 [0.50, 1.62]**	1.54 [−7.09, 10.16]	0.16 [−0.38, 0.69]	4.38 [−4.25, 13.01]	0.45 [−0.09, 0.99]
Mental health	3.59 [−3.15, 10.34]	0.37 [−0.17, 0.91]	6.52 [−0.22, 13.27]	**0.67 [0.12, 1.22]**	4.10 [−2.80, 11.01]	0.42 [−0.12, 0.96]	6.81 [−0.28, 13.90]	**0.70 [0.15, 1.25]**	−2.42[−10.39, 5.55]	−0.25 [−0.79, 0.30]	0.29 [−7.88, 8.46]	0.03 [−0.51, 0.57]
STAI												
Trait anxiety	−3.89 [−8.14, 0.37]	−0.38 [−0.92, 0.16]	**−7.39 [−11.64, −3.14]**	**−0.71 [−1.27, −0.16]**	**−6.34 [−10.70, −1.98]**	**−0.61[−1.16, −0.07]**	**−7.66 [−12.00, −3.29]**	**−0.74 [−1.29, −0.19]**	1.05 [−3.92, 6.02]	0.10 [−0.44, 0.64]	−0.26 [−5.23, 4.71]	−0.03 [−0.57, 0.52]
State anxiety	**−7.04 [−12.90, −1.17]**	**−0.67 [−1.21, −0.12]**	**−8.97 [−14.83, −3.10]**	**−0.85 [−1.41, −0.29]**	**−7.07 [−13.08, −1.06]**	**−0.67[−1.22, −0.12]**	**−8.00 [−14.01, −1.99]**	**−0.76 [−1.31, −0,21]**	1.89 [−5.00, 8.78]	0.18 [−0.36, 0.72]	0.97 [−5.92, 7.86]	0.09 [−0.45, 0.63]
BDI-II												
Total	**−4.01 [−7.42, −0.69]**	**−0.61 [−1.15, −0.07]**	**−5.72 [−9.13, −2.31]**	**−0.87 [−1.43, −0.31]**	**−5.68 [−9.17, −2.18]**	**−0.86 [−1.42, −0.31]**	**−5.68 [−9.17, −2.18]**	**−0.86 [−1.42, −0.31]**	0.05 [−3.95, 4.05]	0.01 [−0.54, 0.56]	0.05 [−3.95, 4.05]	0.01 [−0.54, 0.56]

LMM, Linear mixed model; MD, Mean difference; SMD, Standardized mean difference (Hedge's g); IBSSI, Irritable Bowel Syndrome Severity Index; VSI, Vischeral Sensitivity Index; IBS-QOL, Irritable Bowel Syndrome-Quality Of Life. Bold values indicate statistically significant mean differences based on a P < 0.05 level and their 95% confidence intervals.

$g = 1.20$ (0.62, 1.78)], and from baseline to 6-month follow-up [Hedges' $g = 1.19$ (0.61, 1.78)].

The total score of IBS-QOL improved significantly from baseline to mid-treatment, post-treatment, 3-month follow-up, and 6-month follow-up. The effect size of the IBS-QOL was large from baseline to mid-treatment [Hedges' $g = 1.04$ (0.46, 1.61)], post-treatment [Hedges' $g = 1.73$ (1.1, 2.36)], 3-month follow-up [Hedges' $g = 1.75$ (1.12, 2.38)], and 6-month follow-up [Hedges' $g = 1.67$ (1.05, 2.29)].

The subscales of IBS-QOL, such as dysphoria, interference with activity, body image, health worries, food avoidance, social reaction, and relationships except for sexual concerns, improved significantly from baseline to mid-treatment or post-treatment, 3-month, and 6-month follow-up. The effect size of the subscales of IBS-QOL was medium to large from baseline to post-treatment, 3-month follow-up, and 6-month follow-up (see **Table 5**, **Appendices 1**, **2**).

In the SF-36 subscales, the effect size of "role physical" was large from baseline to each follow-up, "role emotional" was large from baseline to 6-month follow-up, and "mental health" was medium from baseline to post-treatment and 6-month follow-up (see **Table 5**).

In STAI, "state anxiety" improved significantly from baseline to mid-treatment, post-treatment, 3-month follow-up, and 6-month follow-up. The effect size of "state anxiety" was large from baseline to post-treatment [Hedges' $g = -0.85$ (−1.41, −0.29)].

The total score of BDI-II improved significantly from baseline to mid-treatment, post-treatment, 3-month follow-up, and 6-month follow-up. The effect size of the total score of BDI-II was large from baseline to post-treatment [Hedges' $g = -0.87$ (−1.43, −0.31)], 3-month follow-up [Hedges' $g = -0.86$ (−1.42, −0.31)] and 6-month follow-up [Hedges' $g = -0.86$ (−1.42, −0.31)] (see **Table 5**).

Responder Status

The responder rate in the IBSSI-J at post-treatment was 42.9% (6/14), at the 3-month follow-up was 53.8% (7/13), and at the 6-month follow-up was 53.8% (7/13). Meanwhile, the responder rate in the VSI at post-treatment was 57.1% (8/14), at the 3-month follow-up was 69.2% (9/13), and at the 6-month follow-up was 69.2% (9/13). The IBS-GIS responder rate in this study was 68.8% at post-treatment, 50% at the 3-month follow-up, and 56.3% at the 6-month follow-up.

Adverse Events

There were no severe adverse events throughout the interventions.

DISCUSSION

We developed a hybrid CBT-IE, which we demonstrated to be a safe and feasible intervention method and acceptable treatment for refractory IBS in Japan. Notably, the hybrid CBT-IE induced a statistically significant change in IBSSI-J scores and most of the secondary outcomes, except some subscales of SF-36, with a medium-to-large effect size in patients with IBS. Specifically describing the potential of hybrid CBT-IE, we concluded that the severity of IBS, visceral anxiety, IBS-specific health-related QOL, state anxiety, and depression could improve in the medium to long term. In addition, the dropout rate for failure to complete the 10 sessions was low and no significant adverse events were observed.

Responder rates were comparable to our previous face-to-face only CBT-IE feasibility study. In the previous study (20), participants were diagnosed with IBS by Rome III with moderate to severe symptoms ($N = 20$). In addition, the responder rates in the IBS-GIS were also comparable to our previous face-to-face only feasibility study (20).

The hybrid CBT-IE was not inferior to, less effective, less feasible, or less safe than the face-to-face only CBT-IE. There was no difference in dropout and responder rates in the IBSSI-J and IBS-GIS in all assessment points between the two forms of CBT-IE (21), proving that the hybrid CBT-IE program did not negate the beneficial effects while halving the session time compared to the face-to-face only CBT-IE. In particular, the primary endpoint IBSSI-J decreased with a mean difference of 121.22 (95% confidence interval 68.84–173.61), which was slightly below a change score of 50% as a benchmark of clinical improvement (24). Furthermore, the minimal clinically important difference (MCID) of the total score of the IBS-QOL was between 10 and 14 (33). The mean difference of the IBS-QOL in this study was 26.77 (95% confidence interval 17.49–36.05), which was higher than the value of the MCID of the IBS-QOL. We speculate that the patient's preparation using the video material in advance helped both the patient and therapist focus more on developing the patient's adaptive cognitive behavioral skills in the subsequent face-to-face session. We also found that our hybrid CBT-IE seemed to reduce symptom recurrence more than the face-to-face only CBT-IE in the long-term 6-month follow-up (34).

The beneficial aspects of both CBT-IE and video materials were merged in the hybrid CBT-IE without discarding either. Previous studies have suggested that the presence or absence of therapist direction in CBT sessions is related to effectiveness (35), and this finding is supported by our current results. Hybrid CBT-IE is expected to make it easier for patients to implement *in vivo* exposure as well as IE to situations and sensations they fear and avoid (18, 36, 37); it is often difficult to do so without the direct or indirect guidance of a therapist. In addition, the video materials can be used as a teaching aid for therapists unfamiliar with IBS, which may make it easier for them to implement CBT-IE. Thus, the hybrid CBT-IE can be implemented while retaining the best features of face-to-face only CBT-IE.

We describe the possible future development of CBT for IBS and the hybrid CBT in the post-COVID-19 era. Recently, in the field of CBT for IBS, a randomized controlled trial (RCT) was conducted to assess clinical responses to home-based minimal-contact CBT (MC-CBT) compared with clinic-based standard CBT. MC-CBT minimizes the frequency of visits to medical facilities (38). It consists of psychoeducation, relaxation, cognitive restructuring, problem solving, and relapse prevention, with only four face-to-face meetings with a therapist of 50 min each and home study materials to cover the same procedures as clinic-based-CBT. It has been suggested by Lackner et al. that 10 sessions of clinical-based standard CBT does not appear to provide an incremental advantage over four sessions of home-based CBT, despite a 60% reduction in the time required by clinicians. Meanwhile, it has been noted that MC-CBT has a slower onset of therapeutic effect than standard CBT (39). With the current COVID-19 pandemic, based on the aforementioned advantages and disadvantages of MC-CBT, it may be necessary to study how far we can reduce the number of face-to-face sessions for a hybrid CBT-IE in the future, to the extent that exposure can be properly implemented. In addition, an RCT of group therapy has been performed for CBT-IE in Japan, and the results are awaited (40).

To confirm the effectiveness of the hybrid CBT-IE, we are conducting a multicenter, parallel-design randomized control trial (23). We need to increase the number of participants and investigate the mechanisms of the hybrid CBT-IE, focusing on attentional function, changes in dysfunctional thinking (e.g., catastrophic thoughts), and reducing the use of safety behavior and safety signals included the hybrid CBT-IE.

Limitations

Four limitations of this study should be noted. First, this study had an open-labeled, single-arm design. The symptom reductions observed in this study are difficult to distinguish from remission seen during normal treatment. However, improvement scores shown in not only the IBSSI-J but also the IBS-QOL had higher values than those in the placebo in the RCT of the drug development (33, 41). Caution must be exercised in interpreting the results due to the small sample size and single-group nature of our study, and further validation is an issue for the future. The hybrid CBT-IE seems to be worth analyzing in an RCT. Second, a single facility participated in this study. It is possible that the results were affected by this design (42). Ideally, therapists from multiple and diverse backgrounds should have participated in the study to disseminate the hybrid CBT-IE widely with the aim of achieving a certain level of effectiveness regardless of which therapist implemented it. Third, we did not examine participants' learning effect to check whether the follow-up results were influenced by reviewing the video materials and other materials after the intervention was completed. We suggest that the learning effect using psychoeducational materials needs to be examined. Fourth, this study was not originally designed as a non-inferiority study, and thus, the results should be interpreted with caution.

CONCLUSIONS

This study examined the feasibility and efficacy of the hybrid CBT-IE for refractory IBS in Japan. The results indicated that the dropout rate in this study was comparable to our previous face-to-face only CBT-IE. It was also suggested that the hybrid CBT-IE was effective and could be conducted safely; it is potentially effective for improving IBS severity, visceral anxiety, and QOL.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee in National Center of Neurology and Psychiatry, Tokyo, Japan. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TA was the primary investigator and conducted this study. TA, YF, HK, CO, and NS designed this study. YO, SK, MH, and TA developed the Japanese version of CBT-IE and its psychoeducational materials. YF and TA developed the video materials. TA, YT, and HA recruited and screened participants. HitK and MF conducted the interventions and corrected data. KH did data entry. MF and KM analyzed the data. TA, YF, AS, and SF supervised the overall conduct of the study. The initial draft manuscript was written by MF. All authors read and approved the final manuscript to be published.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.673939/full#supplementary-material

Appendix 1 | Inference results for fixed effects LMM.

Appendix 2 | Inference results for covariance parameters LMM.

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Life Events and Adaptive Coping Approaches to Self-Management From the Perspectives of Hospitalized Cardiovascular Patients: A Qualitative Study

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Objectives: This study aimed to explore the association between hospitalized cardiovascular patients' life events and adaptive coping approaches to self-management.

Methods: The study was a qualitative study that was conducted in a cardiology department of one affiliated university hospital in Hangzhou, China. Twenty-eight participants with cardiovascular diseases were recruited through a purposive sampling procedure. Semi-structured interviews were used to gain insights into adaptive coping approaches to self-management when living with different life events. Interviews were audio-recorded and transcribed, and the data were analyzed by thematic analysis.

Results: Life events reported by hospitalized cardiovascular participants could be summarized in four categories: daily routines, life changes, life-threatening experiences, and emotional sufferings. The adaptive coping approaches were also summarized in four themes: decision-making, avoidance, consistent responses, and episodic responses.

Conclusion: This study described essential insights into the mutual influences between various life events and adaptive coping approaches to self-management by a group of hospitalized cardiovascular patients. Participants coped with their problems flexibly by processing comprehensive information from various and unpredictable life events regarding the situations and contexts. While inequity was cumulated, psychological resilience was a vital mediator between stressful events and their responses. The study illuminated the importance of understanding context, situations, and experiences on how cardiovascular patients adapted to their self-management regimens.

Keywords: cardiovascular diseases, life events, adaptation, self-management, qualitative research

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INTRODUCTION

Among chronic diseases, cardiovascular disease is one of the leading causes of mortality and results in different kinds of burdens for the government, family, caregivers, and individuals (1–4). Self-management is described as an interactive and everyday process, involving environmental, physical, mental, and other domains, which is widely recognized as a convenient and economical method to monitor chronic diseases and maintain a satisfactory quality of life (5–7). However, despite effectiveness of self-management, it is dynamic, depending on the stages or phases of cardiovascular disease and other kinds of changes in the patient's life situations and contexts (8). Thus, to improve the quality of life, cardiovascular disease patients should accordingly adjust their self-management strategies over time across their life span.

Life events occur in a real-world setting and accumulate during the life span, which has a great impact on individuals' well-being, health, and behaviors; and evidence in the literature has shown that stressful life events are highly correlated with disease and health outcomes, which could be defined by epidemiological, psychological, and biological traditions (9). Therefore, coping with different life event situations is an essential part of long-term life adaptation to kinds of human diseases (10–12). Besides, resilience represents coping and rising above difficult experiences, indicating the capacity of a person to successfully adapt to change after stressful situations and resume the previous so-called healthy conditions psychically and mentally (13). Self-management is a complex set of various life events and includes not only the normative aspects but also the stressful challenges. Studies have previously investigated the relationship between stressful life events and self-management within some populations with chronic diseases (e.g., diabetes, metabolism, and chronic obstructive pulmonary disease), like groups of children and old rural patients (14–16). As for cardiovascular disease, quantitative studies have examined the coping strategies (17), as well as their associations with anxiety and physical functioning in heart failure groups (17, 18). And there were also qualitative studies exploring life experiences and coping strategies in patients with heart diseases (19–21). A longitudinal qualitative study has developed four chronic illness self-management patterns over time from a broad perspective (8) but did not specifically introduce the relationship between life events and self-management. Researchers have found that the use of maladaptive coping strategies can divert attention from heart failure among older patients (22). A literature review taken by Li and Shun (23) has discussed the coping styles of patients with chronic heart failure, like emotion-focused and problem-focused coping, but it did not explore all types of cardiovascular patients. Moreover, another qualitative meta-synthesis integrated information supporting coping and adaptation of left ventricular assist device (LVAD) patients, which had four stages including different tasks in physical, psychological, and social domains (24).

Although there were several studies that have explored the relationship between coping and life events, there is little known about the coping strategies for living with cardiovascular diseases in samples of Chinese hospitalized patients. Thus, capturing these aspects from the participants' viewpoints is necessary for tailoring interventions that could promote better self-management adaptation effectively in cardiovascular groups. Hence, this study aimed to explore the patients' life events and adaptive coping approaches to self-management when living with cardiovascular diseases.

METHODS

Design

A qualitative design was applied, which aimed to explore cardiovascular patients' life events and their adaptive coping approaches for self-management. Semi-structured interviews were chosen to collect rich data. Thematic analysis (25) was used to extract the themes and develop results to learn more about patients' adaptive coping strategies for self-management when living with their chronic cardiovascular conditions.

Setting and Sampling

The study was undertaken in a cardiology department of one affiliated general university hospital with 2,400 beds in Hangzhou, China. After the authors obtained permission to enter the department from the Nurse Deputy Director and Department Nursing Directors, study recruitment began.

A purposive and criterion-based sampling procedure was used to recruit patients with rich information. The criteria selecting the participants were included as follows: (1) aged 18 years or older; (2) living with chronic diseases over 6 months and having at least one cardiac event; (3) willing to share their experiences and to express themselves clearly; (4) volunteered to provide informed consent; and (5) has no involvement in other studies at the same time. Nurses in the recruitment site assisted in identifying eligibility, including registration information and medical history. Potential participants' names and bed numbers were collected, and then nurses informed them about the study. The specific time that authors contacted potential informants depended on the availability of patients and/or their families, usually after daily ward rounds. Considering the time constraints of staying in the department, when researchers found no more new valuable information and data reached information saturation, they had a discussion to achieve a consensus on the time point of stopping recruitment and leaving the field. Thus, a total of 32 patients under hospitalization were invited, and 29 persons agreed to participate in the study. One female patient refused the invitation because she wanted her disease to be kept a secret. Six invitations were sent to participants' family members, and two of them rejected the invitation directly. Moreover, one male patient finished the interview but was still excluded owing to the complicated dialect. As a result, data comprising 28 participants were finally analyzed.

Data Collection Procedure

Selected individuals received an information letter inviting them to participate in the study and an oral introduction of the study before the interviews was carried out, including the purpose, guarantee of confidentiality, and voluntary principle. They were invited to have face-to-face, in-depth interviews to share personal experiences once they were available. Under the study setting, participants chose a location in the department for their interviews according to individual preference, such as a quiet meeting room or a private corner. Some participants liked to stay in bed with curtains pulled up while receiving the interviews after interventional operations when no ward mates were present in the shared room, where it could be regarded as a relatively private place. Fourteen caregivers accompanied their patients in case of any emergent care needs. Besides, caregivers were only supposed to explain some local dialect expressions for the researchers when needed; otherwise, they were not permitted to influence the interview process.

Data were collected from April to May 2018 by two competent nursing students: one PhD student (RQ) and one master student (QZ). Both of them have received professional training for the techniques about how to conduct qualitative studies. Most interviews were mainly guided by RQ, with QZ as an assistant taking note, except for three interviews conducted by QZ. Based on the Chronic Care Model (26), data collections followed a semi-structured interview guide, which was piloted in patients with chronic diseases at the physical examination center and locally adjusted to have more understandable questions. Before the interviews, all participants were invited to provide informed consent. It was critical to emphasize the aim to learn different perspectives from patients about the research. Interviews started with warm greetings and self-introduction to develop a rapport before proceeding to more sensitive questions. Then questions like "Could you please share your experiences about how you live with cardiac diseases?" or "How do you cope with your body conditions?" aimed to allow participants adequate time to explore their experiences. Several probing questions, such as "Could you please tell me more about that thing you mentioned just now?" and "What did you exactly do when you encountered a severe heart attack," were intentionally asked to encourage participants to clarify descriptions or provide rich information when narratives referred to different contexts and specific events. The questioning was relatively flexible rather than inducing any answers. Participants could use accents and their expressions to generate their stories. The final question was always a form of "Do you think there is anything else I should have asked or do you have anything else to add?" Most interviews took place at the bedside, between 5 and 115 minutes. Two patients (P15 and P19) were informed by the nurse to do examinations and were no longer available for the interview, and one of the interviews (P19) lasted only 5 minutes. However, the two participants, and the 5-min interview, provided rich information so that after consulting the expert and holding a discussion within the team-member group, the two narrative data were kept with the patients' permissions. Interviews were audio-taped and all transcribed verbatim in Chinese. Every participant was assigned a code to guarantee anonymity.

Data Analysis

A thematic analysis was applied in the study according to the method approach recommended by Braun and Clarke (25). Qualitative data could be analyzed by hand or computer software; therefore, RQ, the first author, analyzed the data manually. Owing to the preference for analyzing by hand and a small number of the transcript pages, RQ used color markers to distinguish coding parts of texts. At the beginning of the analysis, the transcripts were read repeatedly for a better understanding, while some basic ideas related to life events and adaptive coping approaches were written down to obtain an overall picture. Then, qualitative data were reviewed in more detail, and text segments were bracketed and narrowed into codes, with the meaningful descriptions. Third, similar codes were separately collated into groups, and the major ones were retained by examining whether they were discussed most frequently by participants, most supportive, or most relevant to our topics. Without a preexisting frame, potential themes or subthemes focusing on life events and coping approaches were developed until no more new evidence provided additional themes. These major themes brought authors' perspectives to make interpretations of collecting qualitative information. Rest codes and candidate themes were made for further decisions to reach an accurate representation. Otherwise, redundancies were eliminated. Finally, clear definitions and detailed descriptions about the identified life events and sorted adaptive coping approaches for self-management were established to fit determined themes (25). During the analysis process, many memos were used for extracting and tracking the initial ideas.

Rigor

To enhance the rigor, there were several strategies. First, having two researchers always present in the interviews, one mainly guiding the interview while the other taking notes, allowed different perspectives and conclusions. Then, opinions from cardiovascular participants with complications or multi-morbidities helped enrich the data source. Third, caregivers playing the roles of dialect interpreters improved the understanding of patients' descriptions. These strategies boosted the triangulation in this qualitative study. Besides, identified themes were discussed with an expert (KS) who had significant cultural differences and reviewed by a third team member (LW) for opinions. Peer review ensured credibility during the process of integrating the data. Furthermore, participants who wanted to know the findings received the transcribed documents and the initial results. In case of discrepancies, member checking was also a good method to solve these problems, and their opinions were considered in the final presentation to help confirm if the authors had specified the themes adequately and accurately.

RESULTS

Patients

There were 21 men and seven women contained in this study, between 32 and 86 years old. All of them were admitted to the hospital due to a cardiac event. Everyone has been diagnosed with hypertension, and some of them also had diabetes, gout, and other chronic conditions. Most of the participants had received an education, and half of them went to college. Most participants were from Zhejiang Province, and some of them were retired. Detailed demographic characteristics are shown in **Tables 1**, **2**.

Life Events

When describing the experiences of living with cardiovascular disease, patients described various life events, which could have occurred before, during, and after the disease diagnosis. Participants thought these events had a positive or negative impact on their self-management concepts and awareness or behaviors.

TABLE 1 | Patients' demographic characteristics.

Variables	Total ($N = 28$)	%
Age		
Mean age	62.50	–
Range	32–86	–
Gender		
Male	21	75.0
Female	7	25.0
Marital status		
Married	24	85.7
Divorced	1	3.6
Widowed	3	10.7
Education		
No formal education	1	3.6
Primary	4	14.3
Secondary	11	39.3
College or university	12	42.8
District		
Zhejiang province	24	85.7
Other provinces	4	14.3
Occupation		
Private	6	21.4
Employed	10	35.7
Retired	12	42.9
Religion		
Christian	4	14.3
Buddhist	2	7.1
Atheist	10	35.7
Not reported	12	42.9
Chronic conditions		
Single cardiovascular disease	8	28.6
Multiple chronic conditions	20	71.4

TABLE 2 | Details about patients' chronic conditions.

Patient	Gender	Age	Chronic condition
1	M	57	D, HL, HT
2	F	56	D, HT
3	F	61	B, CKD, HT
4	M	51	CVD, HT
5	M	52	HT(P)
6	M	79	HT
7	M	62	HT
8	M	34	HT
9	M	48	HT
10	F	70	CVD, HT
11	F	84	CVD, HT
12	M	72	HT, D, CVD
13	M	86	HT, G, CA
14	M	48	HT
15	M	73	HT, D, HL, CVD
16	M	52	HL, HT
17	M	40	D, HT, S
18	F	86	CVD, D, HT
19	M	32	HL, HT
20	F	45	D, HL, HT, S
21	F	79	CVD(P), D, HT
22	M	72	HT(P)
23	M	68	CVD, G, HT
24	M	69	CVD, HT, S
25	M	79	CVD, D, HT, S
26	M	77	HT
27	M	53	CVD, D, HL, HT
28	M	65	CVD, HT

F, female; M, male; B, Behcet syndrome; CA, cancer; CKD, chronic kidney disease; CVD, cardiovascular disease; D, diabetes; G, gout; HL, hyperlipidemia; HT, hypertension; P, pacemaker; S, stroke.

Daily Routines

Daily routines were the most cited statements in participants' narratives. As an almost fixed and frequently happening itinerary on participants' schedules, these kinds of reported events cover the fundamental aspects of daily life and were likely to have exact time points.

Normal Life Activities

Normal life activities referred to the most straightforward behaviors that were tightly related to cardiovascular participants' basic survival, such as eating, entertainment, and working. Several patients mentioned that they would like to have access to medical information through advanced techniques. The younger ones were interested in using mobile devices, while the older ones preferred traditional ways. P28 regarded watching a health-related TV program as a regular activity after work to learn more medical knowledge: "As soon as I get home, I open the TV to watch the 'Meet on the road of Health' every day" (P28, male, 65). In addition, P10 reported that she likes watching health channels. Moreover, reading health magazines was her favorite daily work:

> "We subscribed to a series of medical reading materials. [...] Once we get free time, we will read these magazines. I usually gather those useful information parts, and make them a small scrapbook." (P10, female, 70)

At the same time, even if some participants were over 70 years old, they have received a good education in their youth. Therefore, they could still follow the trend. Well-educated P12 was always enthusiastic about searching on the internet or watching online videos for specialist opinions, and P13 enjoyed connecting with his families and watching videos by pads.

> "I searched for some information about the techniques of coronary arteriography on the internet, and I found two domestic websites, which speak more authoritatively nationwide." (P12, male, 72)

As for eating, those who had more social activities tended to lead a more unhealthy lifestyle. Given that P9 was a driving coach, he used to be invited to have big meals in restaurants after his students obtained licenses. Therefore, in his late forties, he still kept the eating habit, for he thought he was only diagnosed with hypertension rather than other serious diseases: "I enjoy eating those kinds of oily stir-fried dishes, delicious and tasty" (P9, male, 48). Although the youngest informant clearly understood that he was leading an unhealthy life due to his job shift, he was unable to change this situation:

> "If I am not available [for lunch] during shifts, I will just grab a bite to eat, like fried pancakes or other instant food." (P19, male, 32)

Self-Care

Self-care is linked to enhancing a better lifestyle and quality of life. Some of these cardiovascular patients in current study considered that self-care was nested in their daily routines, and was one of the most frequent everyday events. Such events are always combined with normal life activities so that they could have better interactions with the context. Many participants reported that they were used to walking for a while in the early morning or after dinner. For example, a male participant with both diabetes and cardiac diseases told that it was a habit to do so:

> "Sometimes in the morning, well, I get up at 5:00 or 5:30 am. [Take a deep breath] First, have the insulin injected- I should have the meal in half an hour –and then, walk for one and a half hours. Yep, walk, and then eat." (P27, male, 53)

As for receiving acute care during hospitalization, participants said professional health providers and equipment made them rest. Meantime, they had realized the severity of these non-communicable diseases. Thus, it was rather natural for patients to have better performance, especially to follow the regular time of medication and meals, as well as quitting smoking and alcohol consumption. As P23 confirmed surely:

> "After being admitted in the hospital, emm, I absolutely gave up smoking and did not pick it up anymore. And the drinking was also cut out for a long period." (P23, male, 68)

Life Changes

Participants mentioned that they had encountered several significant life changes when living with their diseases, such as starting working, getting married, a family member passing away, and moving. As a successful and confident self-employed person, P1 stated that he always worked here and there, and once he worked and settled in one place, he gradually adapted having a local lighter flavored cuisine than in his hometown: "It was after I came to Hangzhou that I ate less oily food" (P1, male, 57). Except for this, P1 did not keep other dietary habits in check, such as alcohol consumption, and he said he seldom exercised. Although he was worried and aware of the importance of taking care of his body, he was too confident to follow the doctor's suggestions. P8 reported that his life had changed significantly than he expected, like divorcing his wife, his mother being seriously ill, and being a patient. Though life was so harsh, he was still in strong morale to face the difficulties from each aspect:

> "I mean, my health condition's poor and I can't afford any heavy work, which makes me under huge pressure. [...] Health matters to me. Ah! Yea... My wife and I have been divorced, and my child also left me. These are definitely stressful. [...] So what? No matter how big the pressure is, you have to live." (P8, male, 34)

Some uncontrollable events had significant impacts on society, leading to critical political or economic changes. These changes also brought differences to individuals' life, such as social status, financial conditions, and personal values, especially for those participants older than other informants. An old lady narrated a story about how she got hypertension in a political protest during the Cultural Revolution and how she dealt with the problem after that:

> "Due to the human resource shortage, I was assigned to work for the Municipal Government such that I even couldn't take a good rest at that time. [...] Though the blood pressure was still at a high level, I insisted on working rather than asking for sick leave." (P18, female, 86)

Life-Threatening Experiences

Life-threatening experiences were reported to be a crucial time point for patients to realize that health management was related to cardiogenic shock, severe complications, and unexpected side effects. Under this situation, those participants who had unreasonable self-management always expressed their wish to manage themselves better, mainly middle-aged male participants. A participant described his experience as follows:

> "I got a shock within 10 minutes after arriving at the outpatient department by myself, and then I was admitted to the hospital. I was in an unconscious status from February 19th till March 6th. Finally, I woke up, and it was just like a dream." (P4, male, 51)

Any of these emergency situations would occasionally cause severe accidents and threaten participants' lives. Several patients said they had even been on the edge of death. P26 described that he had fallen from the upstairs, due to the dizziness caused by his hypertension: "I felt dizzy at first, and then I rolled down [from the third floor], from upstairs to downstairs" (P26, male, 77). Another event was told by P27: "Last year, I had a car accident, um... it might be a heart attack, yea, caused by a heart attack" (P27, male, 53).

Emotional Sufferings

Almost every participant admitted that they were always involved in emotional fluctuations, especially accompanied by symptom aggravations. Notably, hearing of others' sufferings made them realize that they were in the same position. Hence, they were led by emotions and would make decisions unhesitatingly. A story about how other patients struggled to have high-quality living but had poor outcomes would make them worry and would make their emotions churn. P26 learned lessons from relatives' death caused by a stroke, and shortly afterward, he decided to have a coronary stent to get rid of the horrific result. He acknowledged:

> "My wife's brother had a stroke [and passed away]. [. . .] What if I got a stroke? I am afraid of dying. [. . .] Now, I am so pleased to have the interventional therapy." (P26, male, 77)

Moreover, participants reported they were swept into the vortex of their embittered emotions while going through negative events like denial or rudeness from their attending doctors. In contrast, they said that they would like to behave better after receiving adequate support from professionals, peers, and families. Only seven women were recruited in this study, yet they told more emotional experiences than men. For instance:

> "A doctor might think he humorously informed me, "Well, the disease is life-threatening, and you are extremely in danger!" I was frightened by what he told me. [. . .] The information was true, but it was impolite to tell like that." (P21, female, 79)

Adaptive Coping Approaches to Self-Management

Most patients had to make adjustments related to their life due to the cardiovascular disorder. Based on different situations and event stimuli, potential benefits, and personal preferences, participants would develop optimal approaches to adapt to the current environment and situations. It was a status that patients chose a satisfying choice rather than the best one for themselves. These adaptive coping approaches could be either temporary, long-lasting, continuous, or intermittent.

Decision-Making

Cardiovascular patients admitted that they would gather kinds of information from their previous experiences, practice accordingly, and evaluate effectiveness. Participants with comorbidities tended to prioritize dominant self-management strategies to deal with the severest condition (e.g., myocardial infarction, and stroke), which meant that they could control the most obvious or threatening symptoms rapidly in an effective way; meanwhile, they might put less threatening changes aside (e.g., hypertension and diabetes). These processes generally occurred immediately after participants identified the severity and perceived the importance of adjustment, especially for those who had experienced terrible events. Take P12 as a decision-maker example: he used to bicycle to work and home, but he stopped riding after retirement and was living easy with his grandson. However, later he restarted and gradually strengthened exercising resulting from his glucose level, and at last, he was extremely careful about exercise intensity due to a terrible heart attack he had experienced. From then on, he mainly immersed himself into cardiovascular management:

> "[. . .] I had high fasting plasma glucose which was 7 at first and my wife told me it was not that good. But I didn't care at all. One year later, the value increased to 8 and then up to 9 in the third year. At that time, I was finally in a panic and began to consult for information. [. . .] I acknowledged, uh - they also told me as well- Uh, your diabetes would get better if you strengthened exercising. Later, that the same year, I had sudden angina. After that, I immediately transferred all my attention from diabetes to heart disease. [. . .] Not joking, it was deadly once it was ignored." (P12, male, 72)

Though participants would balance the risks and benefits to make an optimal decision, not all the decisions would prompt action. Several younger male participants even deeply understood the importance of a well-adjusted lifestyle and could have made a better change; nevertheless, they still chose to maintain an unhealthy status to make a living. They did not want to be a burden to the whole family; nor did they want to spend money given by their families. P17 was only 40 years old, but he had heart disease, diabetes, stroke, and other complications, any of which would remarkably influence his normal life, let alone working. Hence, he decided to prioritize his body with his wife's understanding, but he felt ashamed at the same time of being unable to make a living and had to rely on his wife:

> "When I talked about this, I felt ashamed. (Forced smile) [. . .] I don't think of anything else but staying here and improving my health condition. But my wife has to go to work, and there are heavy financial burdens." (P17, male, 40)

P5 had recently undergone pacemaker insertion, and everything had changed fast. Even if his wife expressed her concerns, P5 still insisted he was in his prime: "I am considered to be the mainstay and breadwinner of the whole family" (P5, male, 52). After evaluating their conditions, some of the participants would make self-reflections, and then they would decide and plan for the adjusting frequency or degree of following responses. P4 was almost of the same age as P5 and had more awful experiences than P17—he was admitted into the ICU due to his severe disease conditions—but he did not receive any pressure from the medical expenditures, and as a result, he anticipated to focus more on his health rather than be a headstrong patient:

> "After this unforgettable hospitalization, I must be more compliant with the doctor's suggestions and listen to my wife's advice about eating healthier at home." (P4, male, 51)

In consideration of the long-term self-care condition of the cardiovascular disease, some compliant participants followed physicians' recommendations and recorded their daily results of blood pressure carefully in case there came any unpredictable situations. Thus, patients could have abundant and visible data for considerable decision-making.

> "Sometimes the blood pressure level would drop a lot. Or if you noticed that the medicines didn't work and the value stayed at a high level, and then it was a great time point to ask the physician to change the prescription." (P28, male, 65)

Avoidance

Some participants stated that they avoided practicing self-management regimens knowingly, such as smoking cessation and losing weight, which was recommended by many physicians for cardiovascular patients. They believed these behaviors would not cause any severe symptoms. Moreover, considering their personal preferences, they said they would like to satisfy themselves and would like everything to remain the same rather than perform those behaviors to restrict happiness. For instance:

> "The doctors suggested that I should quit smoking, but it's hard to agree. Once I quit smoking, my life would become meaningless. Besides, the harm of smoking may not be as serious as the doctor said." (P9, male, 48)

In contrast, patients who intended to modify their self-management strategies lacked confidence and were fearful of making a move forward. They described that their desires to make changes were sometimes hindered by those cumulative negative experiences. They reported they had encountered frustrating life events (e.g., unemployment and divorce) or annoying emotional feelings (e.g., denial and sadness) repeatedly during their self-management process. Female informants focused more on emotional description, whereas male participants concentrated more on factual statements. What is more, other uncontrollable factors (e.g., personality and policies) also impacted participants' minds. As a result, it was difficult for them to adapt to the current situation. For example, P17 was leading a smooth life before he lost his job. Soon after unemployment, he was diagnosed with multiple chronic diseases. The participant and his family endeavored to look for a better way to treat his diseases. While managing various conditions, life became tougher, and he lost his temper gradually. Aside from those incidents, he also suffered from several unhappy events when communicating with physicians. Cumulative disappointment and stubborn personality aside from his real economic situation all drove him to reject regular treatment but insist on undergoing folk therapy by himself:

> "We have already got heavy financial burdens. [...] The medical treatment in a top-class hospital would cost a lot, and we didn't have such a massive amount of money to cover the costs. There, it couldn't be better if these folk remedies cured my disease." (P17, male, 40)

Consistent Responses

The patients had insisted on one behavior at a uniform time for years after the diagnosis of cardiovascular diseases without major adjustment, regardless of whether these behaviors were motivated passively or actively, such as regular exercise, periodic physical examination, and timed doctor visit. Patients' consistently compliance with the prescribed medication was the most frequently mentioned response to the treatment. They would willingly follow their doctor's suggestions and comply with the adjustment of the treatment regimen, and this behavior became a natural daily routine. When the disease conditions were under control and self-management benefits were accumulated, participants would strengthen their behavior over time. P16 described: "The doctor suggested that I should take antihypertensive drugs. It has been ten years since I started taking medication" (P16, male, 52). Other common consistent strategies for self-management were measuring blood pressure, eating healthy, and exercising. P22 mentioned his experience of using an electronic sphygmomanometer:

> "Later, my son bought me an electronic one [sphygmomanometer], which is rechargeable and much handier, right? Once press the button, well, the screen will show the heart rate and it can tell you whether the result is in a normal range or not. Everything's displayed quickly and clearly, right? But I always forgot to use it, since I was not familiar with it at first. Eh, and then... I was skilled at measuring blood pressure so that it became my daily habit." (P22, male, 72)

Cardiovascular patients who had multiple chronic used unique self-management regimens to manage their conditions. For P13, as a patient with cardiovascular disease and gastric cancer, his diet should be defatted after the gastrectomy: "I only eat that defatted food at home. [...] My family buy coconut oil especially [for me], just because it can be absorbed by the intestines" (P13, male, 86). For those who had diabetes, blood sugar monitoring and insulin injection also were the main behaviors to perform: "Basically, I use the glucometer to test the blood sugar every day. In general, well... As soon as I get up, I will measure the blood sugar level, which is not over 8; and the level is also under control two hours after a meal, which will not exceed 14" (P26, male, 77).

Episodic Responses

The episodic responses referred to those self-management strategies that patients practiced occasionally, temporarily, or irregularly. Participants reported that they implemented different strategies depending on the surroundings and situations, like behaving distinctively in the medical institution and outside the medical institution. Hospitalization implied that they got acute symptoms and intense side effects; therefore, participants always attached great importance to the various suggestions given by professionals. Patients should have behaved in a good manner for a limited period. Nevertheless, P14 reported he was sincerely thankful for the treatment; however, he still argued with the physician due to a terrible outcome after a half month's hospitalization:

> "I demanded a discharge in half a month because I was not treated in the right way, which contributed to my worse condition. [...] I tried my best to keep a good mood to get rid of the bad effects." (P14, male, 73)

P9 stated that he would follow the advised routines given by professionals while he was not so acquiescent at home. Nevertheless, he admitted he had just secretly eaten in a nearby restaurant: "I have just snuck out for lunch. [...] The meal in the hospital seemed to be oil-free and I didn't have any appetite" (P9, male, 48). For another, P2 acted like a child to attract more attention from nurses, which she never did before: "It's kind of like a submissive kid who would like to follow the nurses" (P2, female, 56). Besides, some patients reported that they would perform well when accompanied by their family, especially those older people who lived by themselves, whether in the hospital or at home.

Additionally, participants were telling contradicting behaviors between home and other places except for medical institutions. P27 was fond of smoking and used to smoke within social contexts, whereas he described his own rule about respective behaviors outside and at home—never smoking in front of his families at home—which became a habit unconsciously:

> "I set myself a rule that no matter how heavily I smoke outside, I don't smoke inside the house. [. . .] From the very beginning of my smoking until I quitted it, as long as I got home, I would naturally stop smoking. [. . .] I would go outdoors [when I am desperate for the nicotine]." (P27, male, 77)

To deal with some specific incidents, participants were expected to perform the coping strategies on demand, like helping themselves when it came to an emergency heart attack or adapting a new health behavior in daily life to get rid of risks. This was practiced occasionally, and the behavior could assist patients in maintaining their long-term health over time. P28 described that he had found the way to protect himself when he felt that they would suddenly faint:

> "If I was about to fall at that moment, I would squat down, which made it safer." (P28, male, 65)

Practicing suggested activities intermittently referred to episodic responses as well. Moreover, even though patients implemented healthier self-management regimens, some impactful events could still trigger patients' previous unadjusted self-management behaviors. These events mainly involved medication non-adherence, overeating, and smoking among male participants. Several participants described their experiences of stopping smoking and return to smoking. Most admitted that smoking due to social needs. P9 had tried to quit smoking three times, but he failed every time, and he made his mind to quit it after discharge. P5 said he had succeeded in smoking cessation. But later, he suffered the tremendous pain of losing his father. It was such a dreadful blow, so he picked cigarettes up to de-stress himself. Nonetheless, he stopped smoking after he got over this sadness:

> "After seven years of quitting smoking, I restarted smoking and kept for another half a year. It has been over five months since my second smoking cessation." (P5, male, 52)

DISCUSSION

Mutual Influences

This study has shown that cardiovascular patients have immersed themselves in daily real-world contexts and experienced kinds of life events. Some repetitive self-management regimens were more like routines embedded into daily lives, and these behaviors were practiced regularly without extra reminders. Repeating the same behavior could strengthen the awareness of the initiative and reinforcement of a healthy habit. However, there have been rare qualitative studies discussing this topic. It is also worth mentioning that electronic devices have played an important role in patients' daily self-management. Patients could get access to a large amount of useful information when they get the urge to know something rather than make appointments with their physicians on selected days. This is more convenient and time-saving. Several older informants were skilled in using electronic products to assist in their self-management in this study. The report of the 41st China Statistical Report on Internet Development (27) showed that not only the young population is fond of browsing websites, but also an increasing number of the elderly are interested in looking for information purposively online. However, information selection requires further abilities, and consulting with a doctor was more reliable (28). In our study, older patients with higher educational backgrounds told more about resource utilization behaviors than those who did not obtain enough education. This implies that the development of technology is gradually adopted by a part of older people with chronic diseases as an appealing and effective cooperator even though there are some barriers (29, 30). On the other hand, there is also evidence that past educational experiences have a profound impact on the future health behaviors of self-management. It is also approved that different vocations affect the outcomes of an anticipated self-management and vice versa, which is obviously seen among the younger male informants in our study. Social expectations regard working as role responsibility within socialization, while body conditions have prevented better working activities due to time of shifts, working places, and work intensity. In line with the findings in a mixed-methods study (31), patients with heart failure continued to work due to socially based values until they were highly symptomatic.

Life changes and life-threatening experiences are both major life turning points, but the differences between them are that the former focus more on the general changing of demographic characteristics and connections with the social environment in a broader perspective, while the latter seem more personally concerned about individuals' adaptation to themselves. As referred to in the interviews, life changes mainly lead to changes in social networks, cultural atmosphere, and socioeconomic status, which are all contextual factors for self-management (32, 33). Life-threatening experiences would affect physical and psychological status. Consistent with Mariola Zapater-Fajarí and her co-workers, the more active psychological states individuals have, the better and more positively they could adapt to the self-management when they faced adverse life events (34). Emotional experiences are kind of slow and cumulative infiltration. Female participants would be more sensitive than males to this type of life experience. They suffered more from the emotional life events, so they used different coping strategies; nevertheless, they still felt unable to release their stress and had a sense of insecurity. In accord with previous studies, they might grow dependent on others and felt guilty for being sick and not correspond to gendered societal expectations (35, 36).

It could be an indication for patients that they should pay more attention to previous events that were imperceptible but have deeply affected them, which helped them understand what is "living with dying." These life events have their repeatability, diversity, and unpredictability, which were associated with the ongoing awareness of mortality in patients living with life-threatening diseases, as the evidence showed in a previous study (37). It was the diversity and unpredictability of diverse life events that led to uncertainty of the health outcomes, and numerous results brought new life events in turn. Allender et al. (38) found that life changes in employment status, residence, physical status, relationships, and family structure could influence the engagement of physical activities that benefited the body conditions, as P1, P18, and P19 mentioned above. As a consequence, mutual influences generated various coping approaches. Therefore, kinds of feedback had been made reflecting patients' perspectives toward life events and the responses on self-management development (39).

Coping Flexibility

This study indicated the importance of recognizing coping flexibility within the cardiovascular population. Four types of adaptive coping approaches were extracted from the qualitative data: decision-making, avoidance, consistent responses, and episodic responses. These four coping approaches do not exist on one own but combine and/or transform mutually. Similar to the results were found from the studies conducted by other researchers (8, 17), and the author Åsa Audulv identified four different types of developmental patterns, which were consistent, episodic, on-demand, and transitional (8). Patients like P12 distinguished event situations to conduct adaptation, on-demand or consistently, which is in keeping with the situation-specific theory applied in heart failure people (40).

In our study, decision-making always happened when patients received adequate stimulation, which triggered patients to undergo adjustment. As noted in previous literature, situation awareness influenced the implementation of the coping response by perceiving and understanding the events (39, 41). When participants realized the change of the environmental factors, had different emotional feelings, or underwent physical changes, they integrated much comprehensive information and resources, combined with previous experiences, prioritized the setting activities, and then made further optimal decisions accordingly. This is a complicated process involving several steps where patients weigh risks and benefits among situations, considering personal preferences and values, and sometimes the most dominant event or situation weighs the most, in support of the review conducted by Bratzke et al. (42). Meanwhile, regarding the adjustment of P12's physical activities and P28's preventative behavior, patient's ability to respond to a similar situation can be advanced, and the coping actions will be faster increasingly. This might be because patients are far familiar with this situation and excluded some inappropriate choices in previous practices, so once practices are abundant enough for patients' training, they could make good and optimal decisions under the current contexts.

Different from the existing literature, avoidance in our study was a relatively positive but autonomously refusing response, rather than negative ideational constriction, behavioral inhibition, and awareness of emotional numbness. Participants reported that this response mostly resulted from the perception of the complexity in self-management complementation, individual preference, personality, and fear of the recapture of awful past experiences. Moreover, due to some exterior factors like policy and financial conditions, patients would choose a reasonable and cost-effective method to adapt to the contemporary conditions rather than the best one, or so-called intentional avoidance. This agrees with the results that avoiding some situations reduces anxiety through the mediating effect of expectancy (43). Patients with cardiovascular disease who kept practicing consistent responses may be on account of the benefits from the behaviors, especially the visible effects, such as the remarkably decreased blood pressure and obvious weight loss. Positive feedback enhanced the motivation to insist on self-management regimens. Another condition is the fact that they realized that their performance in everyday life is under supervision by family caregivers. According to Whitehead et al., surveillance and support from families could create a context of self-management and promote adherence to daily self-care (44). Conversely, some participants would not like to be accompanied by others only if when they perceived they were in an extremely severe body condition, for some were reluctant to seek help and some were reluctant to become a burden (31).

Our examples not only showed that patients have the same approach in different situations but also revealed that patients would have multiple patterns without cross-situational consistency. In accordance with the work of Bratzke et al. and Liu et al. (42, 45), patients would prefer implementing better self-care treatments in the hospital rather than at home due to the availability of resources and less conflicting or confusing recommendations. More specifically, episodic responses are dependent on the roles that patients are playing and the conditions they get. If participants are hospitalized, they receive acute care, rely on caregivers, and have to be empowered, but when they are at home, they appear to have more autonomy and would gain a sense of control to help themselves freely. They are expected to follow every standard routine suggested by health professionals to reach a certain target in the medical institutions, while they only need to manage common symptoms without getting worse once they are outside medical systems. Besides, they could get access to more technical knowledge from the health providers rather than unknowledgeable family members unless they are experts. Also, some participants who experienced contextual disruption to work and family relationships may have a strong perception of the loss of self, while some set a clear boundary between illness-related events and normal life, which were described as the instances of amenable childlike P2 and principled P27. As found by Kralik et al. (46), living with chronic disease is an ongoing process of transition during one's life span, so participants with the chronic disease might lose or reorient themselves or shift self-identity, accounting for their different performance in coping with different life situations. Once patients have adapted to a new role of being vulnerable patients, they would realize that learning to implement preventative behaviors could reduce the horrible result caused by the bothersome chronic conditions and disease symptoms when there terrible incidents happen. As for the very irregular practices of health behaviors, it was showed in this study that no significant effects, no strict adherence, and no continuous stimuli were the reasons why participants were repeatedly adjusting their self-management strategies.

Inequity Accumulation and Psychological Resilience

Once patients experienced too many negative life events, stress would increase and cumulate regarding the demands associated with specific situations and roles. Thus, patients might perform ineffective responses (e.g., defensive avoidance and purposive non-adherence) after inequality accumulation over time (47), especially when patients have poor communication with health professionals, continuous low autonomy, lack of information, and poor financial status. Life events are unpredictable, so the occurrence of these kinds of life events is more challenging to the resilience of patients. P17's avoidance of receiving formal treatment could be attributed to his tremendous financial burdens, poor supportive interactions as well as irritable personality, and high self-esteem, even he is receiving support from his family. In this case, patients might change their consistent responses into episodic responses, even avoid incorporating treatment, as discussed in a meta-analytic review (48). Evidence showed that anxious patients had less resilience and lower self-efficacy but present with higher self-esteem (49, 50).

We also found that those who had positive attitudes might be more willing to acquire more knowledge, learn more skills, make positive reflections, access more resources, and increase confidence to cope effectively with chronic conditions, indicating that psychological resilience mediated past life events and participants' coping approaches. Existing studies (51, 52) suggested that resilience is a remarkable protective factor for adaptability under adverse life events, and it enables cardiovascular participants to perform healthy behaviors, and promoted better outcomes, like resilient individuals P4, P5, and P8. However, P5 resumed smoking to dissolve the stress when hit by his father's passing away, probably resulting from the change in the family structure and social support (53). Not like P17, even though P8, who was of a similar age, suffered from awful life changes and got heavy financial burdens, he still demonstrated his resilience in the face of all the difficulties due to his high self-efficacy. In contrast to the other positive examples in our study, P1 was optimistic and confident to deal with his problems, yet he lacked self-efficacy to engage in self-management programs that benefited his body's health. Otherwise, P1 reported more successful experiences compared with stressful life events.

Implications and Limitations

Everyone has unique and changing life events, and they should be carefully listened to and valued about their actual in-depth perceptions. Further study can focus on one patient's life stories in narrative inquiry to explore the development of the patient's trajectory of self-management adaptation development. It is also a good way for health professionals to develop more personal interventions precisely regarding individuals' past experiences, emotional responses, and preferences in future researches, such as recalling positive personal events of situation simulation or make self-management behaviors schedule into daily routines. Further researches could focus on building the resiliency of cardiovascular individuals by cognitive interventions who experience adverse events and empowering patients with more effective coping approaches as well as enhancement of the quality of life.

There were still several limitations that should be noted. First, the data were only analyzed by the first author but being reviewed by other research members and discussed with an expert with a different cultural background, which enhanced the study reliability. Second, qualitative data did not cover the variation in participants' self-management descriptions due to the small sample size, as well as the single recruitment site and a short period. The hospital setting might only provide a partial perspective to self-management. Additionally, individuals with cardiovascular diseases were recruited without specific illness diagnoses or trajectories. Further perceptions could be explored by targeting patients with a single cardiac disease. The dataset could be enriched by increasing recruitment sites and carrying out multiple interviews. Using the ethnographic data collecting method would generate more culture-based narratives. Patients speaking rare dialects always lack attention and understanding. Further studies could mainly focus on these groups to explore their insights about self-management. Moreover, the researchers could select participants and analyze the results regarding the disease definitions and classifications. Also, the focus group could improve the interaction and then develop more information.

CONCLUSION

In conclusion, this study has provided essential insights into various life events and adaptive coping approaches for self-management reported by a group of hospitalized cardiovascular patients. Cardiovascular patients have a diversity of life events with unpredictability and uncertainty. There is a mutual influence between life events and adaptive coping approaches: the latter is developing from the former due to the diversity and unpredictability. When experiencing different life events, patients would cope flexibly regarding their situations and contexts. Due to the inequity accumulation of kinds of life events, patients will use their psychological resilience to mediate their especially emotional stress to perform adaptively through positive and negative responses. This study illuminated the importance of understanding the context, situations, and experiences about how cardiovascular patients adapt to their self-management regimens.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available to protect the privacy of the participants. Requests to access the datasets should be directed to Ruolin Qiu, 11518289@zju.edu.cn.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee, Sir Run Run Shaw Hospital, affiliated with the Zhejiang University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZY and LT: conceptualization. RQ: formal analysis, investigation, and writing—original draft preparation. LT: resources, project administration, and funding acquisition. RQ and XW: data curation. RQ and ZY: writing—review and editing. ZY: supervision. All authors approved the submitted version.

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A Study on the Correlations of Anxiety and Depression With Self-Management Ability and Endogenous Creatinine Clearance Rate in Renal Transplant Recipients

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Objective: To explore the effects of anxiety and depression on the self-management ability and endogenous creatinine clearance rate of renal transplant patients.

Method: Eighty-eight renal transplant recipients who were followed up in the outpatient clinic of the Affiliated Hospital of Zunyi Medical University were selected using convenient sampling. The self-made general data sheet, Self-Rating Anxiety Scale, Self-Rating Depression Scale, and Self-Management Scale for Kidney Transplant Recipients were used. Correlation analysis was used to find factors related to endogenous creatinine clearance, while multiple linear regression was used to identify factors influencing endogenous creatinine clearance. Patients with or without anxiety and depression were divided into groups, and the indexes of the groups were compared using the independent samples *t* test, rank-sum test, or chi-squared test.

Results: Anxiety was present in 12.5% of patients, depression in 25%, and a moderate level of self-management in 34.1%. Only 9.1% of renal transplant recipients had endogenous creatinine clearance within the normal range, and 34.1% had a body mass index not in the normal range (25% were overweight, and 9.1% were underweight). The endogenous creatinine clearance rate was negatively correlated with age and degree of depression, and positively correlated with body mass index, treatment management score, and psychosocial management score. The main influencing factors of endogenous creatinine clearance rate were age, sex, depression, body mass index, and treatment management score. The endogenous creatinine clearance rate and psychosocial management ability were significantly higher in patients without anxiety and depression than in patients with anxiety and depression (all $P < 0.05$).

Conclusions: Anxiety and depression showed significant negative effects on the psychosocial self-management ability and endogenous creatinine clearance rate of renal transplant recipients and thus should be given more attention.

Keywords: anxiety, depression, self-management, creatinine clearance rate, renal transplant recipients

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INTRODUCTION

Renal transplantation is currently recognized by the international medical community as the best treatment for patients with end-stage renal disease that can significantly improve survival and quality of life (1, 2). However, while patients benefit from the procedure, they also face many challenges, such as the need to make immunosuppressants for a long time and undergo regular monitoring, occurrence of rejection reactions, and risk of infection after transplantation (3). They also experience higher incidences of diabetes, tumor, and other comorbidities (4, 5). Therefore, a series of self-management programs are required after renal transplantation, and an important guarantee for long-term survival and good quality of life in kidney transplant patients is good self-management. Kidney transplant recipients are also prone to anxiety, depression and other negative emotions after surgery, which can affect the recovery and prognosis of patients (6). Arapaslan et al. (7) have shown that 50% of renal transplant recipients experience anxiety and 25% experience severe depression after surgery. However, the associations of anxiety and depression with self-management and renal function have not been well documented. Endogenous creatinine clearance is a crucial index to assess the damage of glomerular filtration function and evaluate renal function. At present, it has replaced the glomerular filtration rate as the standard for staging chronic renal insufficiency in clinical practice.

Thus, anxiety and depression can severely affect the recovery of renal function of renal transplant recipients, and adequate self-management is critical for renal survival and long-term quality of life of renal transplant recipients. To date, we have not found research on the relationship between anxiety, depression, self-management, and endogenous creatinine clearance in renal transplant recipients.

This study therefore aimed to explore the correlations of anxiety and depression with self-management and endogenous creatinine clearance in renal transplant recipients. Our findings could faciliate future interventions to better improve postoperative quality of life and achieve optimal health outcomes in these recipients.

MATERIALS AND METHODS

Participants

Renal transplant recipients from the outpatient department of the Affiliated Hospital of Zunyi Medical University were selected using convenience sampling between June 2020 and December 2020. The inclusion criteria were as follows: patients who received their first allogeneic kidney transplant; age of $\geq$18 years; kidney transplantat time of $\geq$1 month; patients with communication and reading comprehension abilities. Patients with previous mental illness, patients who were taking antidepressants, patients who were experiencing other diseases affecting self-care, and patients with multiple organ transplants were excluded. All patients enrolled in this study volunteered to participate.

Tools

General information: The general data sheet of kidney transplant recipients was designed by the researchers according to the purpose of the study and mainly included the patients' height, weight, marital status, educational level, occupation, economic status, payment method for treatment, and serum creatinine value.

Anxiety level: We used the Self-rating Anxiety scale (SAS) (8), which consists of 20 items scored in a scale of 1–4: 1 = no or little time, 2 = a small part of time, 3 = considerable time, and 4 = most or all of the time. The higher the SAS score, the higher the anxiety tendency. Based on this score, the degrees of anxiety were divided into three levels: mild anxiety (SAS score 50–59), moderate anxiety (SAS score 60–69), and severe anxiety (SAS score >69). The SAS has good reliability and validity, with Cronbach's alpha coefficients above 0.75.

Depression level: The Self-Rating Depression Scale (SDS) (9), has 20 items, and the scoring formula is the same as that of the SAS. The higher the score, the higher the tendency of depression. According to the score, the degree of depression was divided into three grades: 53–62 for mild depression, 63–72 for moderate depression, and >72 for severe depression. The SDS also has good reliability and validity, with Cronbach's alpha coefficients above 0.75.

Self-management ability: We used the Self-Management for renal transplant recipients (10), which consists of 28 items and the following four dimensions: diet management, treatment management, physical activity management. Each item adopts a four-level scoring system of 1–4, and the total score is 112. The higher the score, the better the self-management ability of the renal transplant recipients. A score of <68 indicated poor self-management ability, 68–90 medium self-management ability, and >90 good self-management ability. The scale has good reliability and validity, with a content validity index of 0.928 and a total Cronbach's alpha coefficient of 0.899. For each subscale, Cronbach's alpha coefficients range from 0.725 to 0.783 (all > 0.7), showing good internal consistency.

Endogenous creatinine clearance is calculated by the following: Endogenous creatinine clearance rate (CCR) = $\{[140 - \text{age (years)}] \times \text{body mass (kg)}\}/[0.818 \times \text{serum creatinine (Scr) } (\mu\ \text{mol/L})]$, and the calculation result for women × 0.85. In adults, if the endogenous creatinine clearance rate is below 80 ml/min, the glomerular filtration function is decreased; reduced to 70∼51 ml/min, mild damage; reduced to 50∼31 ml/min, moderate damage; reduced to below 30 ml/minute, severe damage; reduced to 20∼10 ml/min, early renal insufficiency; reduced to 10∼5 ml/min, late renal insufficiency; and less than 5 ml/min, end-stage renal insufficiency. To obtain the BMI, the following equation is used: BMI = weight (kg)/(height × height) (m). According to the national standard for judging adult weight (National Health and Family Planning Commission of the people's Republic of China, 2013), BMI was divided into four groups: thin (BMI < 18.5), normal (18.5

Abbreviations: CCR, creatinine clearance rate; SAS, Self-Rating Anxiety Scale; SDS, Self-rating Depression Scale.

≤ BMI < 24), overweight (24 ≤ BMI < 28), and obese (BMI ≥ 28).

Procedure

This study was approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University (approval number, KLLY-2020-013). Trained renal transplantation follow-up nurses conducted an on-the-spot questionnaire survey of renal transplant recipients who met the inclusion criteria. The patients were informed about the purpose and content of this study in an anonymous, confidential, and voluntary manner. The questionnaire was distributed on the spot and recycled on the spot. A total of 88 questionnaires were sent out, and all of them were collected (effective recovery rate of 100%).

Statistical Analysis

Count data were expressed as frequencies and percentages, and measurement data as means and standard deviations. Rank variables were analyzed with Spearman's correlation analysis, and continuous variables with Pearson's correlation analysis. We analyzed factors related to endogenous creatinine clearance using multiple linear regression to identify the factors influencing endogenous creatinine clearance. At the same time, differences in the endogenous creatinine clearance rate and self-management ability between the anxiety non-anxiety groups, and between depression and non-depression groups were compared. Measurement data with a normal distribution were compared using the independent samples *t*-tests, Measurement data with a normal distribution were expressed as M (P25, P75), and the rank-sum test was used for intergroup comparison. The classified variables were expressed by frequency and percentage, and the chi-squared test was used for comparison between groups. The difference was statistically significant when $P < 0.05$. All statistical analyses were performed using SPSS 18.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 88 participants were enrolled in this study. **Table 1** reports the demographic characteristics of the participants, including their age, marital status, education, income, and mode of payment for treatment. The average age of the participants was 39.03 ± 11.00 years. The mean follow-up time was 23.70 ± 12.26 months.

The SAS, SDS, and self-management ability scale scores of the renal transplant patients indicated the following: 11 (12.5%) participants experienced anxiety [10 (11.4%) with mild anxiety and 1 (1.1%) with moderate anxiety] and 22 (25%) experienced depression [16 (18.2%) with mild depression and 6 (6.8%) with moderate depression]. Furthermore, there were 30 (34.1%) participants with a medium level of self-management. The self-management scores for diet, treatment, physical activity, and social psychology were 3.36 ± 0.42, 3.56 ± 0.32, 3.31 ± 0.42, and 3.10 ± 0.49, respectively. The specific scores of each scale are shown in **Table 2**.

The average endogenous creatinine clearance rate of the included patients was 64.79 ± 22.55, among which, only 8 (9.1%) patients had normal creatinine clearance rate, 12 (13.6%) had CCR < 80 ml/min, 35 (39.8%) had CCR = 50–70 ml/min, 30 (34.1%) had CCR = 31–50 ml/min, and 3 (3.4%) had CCR < 30 ml/min. The average BMI was 21.96 ± 3.13, in which 58 (65.9%) patients had a body weight within the normal range. Among the patients, 22 (25%) were overweight, of whom 2 (2.2%) were obese. There were 8 (9.1%) patients who were underweight.

The results of the correlation analysis showed that there was no correlation between endogenous creatinine clearance and degree of anxiety in patients. Endogenous creatinine clearance was negatively correlated with age and degree of depression,

TABLE 1 | Patients' demographic characteristics ($n = 88$).

	Number of patients	Proportion (%)
Sex		
Male	58	65.9
Female	30	34.1
Marital status		
Unmarried	14	15.9
Married	71	80.7
Divorced	2	2.3
Widowed	1	1.1
Education		
Primary school	4	4.5
Middle school	25	28.4
High school	24	27.3
Bachelor's degree	35	39.8
Monthly income (yuan)		
0–2,000	36	40.9
2,001–4,999	19	21.6
5,000–7,999	25	28.4
≥8,000	8	9.1
Payment method		
Medical insurance	81	92
At one's own expense	4	4.5
Others	3	3.4

TABLE 2 | Scores of the Self-Rating Anxiety Scale, Self-Rating Depression Scale, and Self-Management Scale for Kidney Transplant Recipients ($n = 88$).

Scale	Minimum	Maximum	Total ($X \pm s$)
SAS	25	70	41.65 (mres)
SDS	32	67.5	47.42 (mres)
Self-Management Scale			
Diet	21	36	30.26
Treatment	26	40	35.64
Physical activity	10	20	16.58
Psychosocial	6	16	12.43
Total score	70	111	94.91

SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; Diet, diet management score; Treat, treatment management score; Physical activity, physical activity management score; Psychosocial, psychosocial management score.

TABLE 3 | Analysis of the correlations of endogenous creatinine clearance and self-management with anxiety and depression.

	CCR	Age	BMI	D	T	SP	PA	Total	Anxiety	Depression	Sex
CCR	1										
Age	−0.337**	1									
BMI	0.260*	0.091	1								
D	−0.015	0.115	−0.132	1							
T	0.254*	−0.083	−0.081	0.648**	1						
PS	0.243*	−0.199	−0.096	0.343**	0.492**	1					
PA	0.084	−0.096	−0.071	0.750**	0.752**	0.482**	1				
Total	0.152	−0.046	−0.118	0.875**	0.885**	0.631**	0.895**	1			
Anxiety	−0.153	−0.021	−0.088	−0.088	−0.16	−0.384**	−0.228*	−0.224*	1		
Depression	−0.264*	0.003	−0.101	−0.053	−0.192	−0.395**	−0.152	−0.206	0.760**	1	
Sex	−0.255*	0.103	−0.18	0.032	−0.015	0.061	0.085	0.04	−0.205	−0.104	1

*CCR, creatinine clearance rate; BMI, body mass index; D, diet management score; T, treatment management score; PS, psychosocial management score; PA, physical activity management score; Total, total score of the self-management scale; Anxiety, patients with anxiety. Depression, patients with depression. *$P < 0.05$, **$P < 0.01$.*

TABLE 4 | Multiple linear regression of factors influencing endogenous creatinine clearance.

Factor	B	SE	β	t	P
(Constant)	39.407	34.895		1.129	0.262
Age	−0.66	0.188	−0.322	−3.516	0.001
BMI	1.782	0.673	0.248	2.649	0.01
Treatment management	1.397	0.64	0.203	2.183	0.032
Depression	−0.533	0.227	−0.219	−2.34	0.021
Sex	−9.345	4.412	−0.198	−2.118	0.037

$R = 0.577$, $R^2 = 0.333$. After adjustment: $R^2 = 0.292$, $F = 8.170$, $P < 0.001$. SE, standard error.

and positively correlated with body mass index, treatment management score, and psychosocial management score. The point-two-column correlation coefficient with sex was −0.255 (**Table 3**).

Endogenous creatinine clearance was taken as the dependent variable, and six statistically significant variables (age, sex, depression, body mass index, treatment management score, psychosocial management score) in the correlation analysis and univariate analysis were taken as independent variables. The results of the multiple linear regression analysis showed that age, sex, depression, body mass index, and treatment management scores were the main influencing factors of endogenous creatinine clearance which accounted for 33.3% of the total variation (**Table 4**).

In the comparison of the self-management ability between patients with anxiety and depression and those without anxiety and depression, the age, body mass index, and endogenous creatinine clearance rate followed a normal distribution. Using the independent samples *t*-test, we found that the age and body mass index of patients with anxiety and depression were higher than those without anxiety and depression; however, the difference was not statistically significant ($P > 0.05$). The endogenous creatinine clearance rate in the anxiety and depression groups was significantly lower than that in the non-anxiety group and depression groups, and the difference was statistically significant ($P < 0.05$) (**Figure 1**). The total score of the self-management scale and the score of each dimension did not follow a normal distribution, which was expressed by M (P25, P75). When the rank-sum test was used to compare the groups, the results showed that the scores for diet management, treatment management, physical activity management, and psychosocial management and the total score of self-management scale in the anxiety and depression groups were lower than those in the non-anxiety and depression groups. However, only the dimension of psychosocial management showed a statistically significant difference ($P < 0.05$). Sex, payment method for treatment, educational level, and monthly income were expressed in terms of frequency and percentage. When the groups were compared using the chi-square test, the results showed that the proportion of patients with high school education and above in the non-anxiety group (71.3%) was significantly higher than that in the anxiety group (36.2%), and the proportion of patients with health insurance payments in the non-anxiety group (94.8%) was significantly higher than that in the anxiety group (72.7%). The proportion of patients with high school education and above in the non-depression group (75.7%) was significantly higher than that in the depression group (40.8%), and the difference was statistically significant (all $P < 0.05$) (**Table 5**).

DISCUSSION

Studies have confirmed that after organ transplantation, 20–60% of recipients experience anxiety, depression, or psychosocial pain (11). In our study, the percentages of patients with anxiety and depression were 12.5% and 25%, respectively, which are higher than those reported by Czyzewski et al. (11.3 and 11.9%, respectively) (12) and lower than those reported by Gök et al. (84 and 66%, respectively) (13, 14).

Our research showed that both anxiety and depression could lead to a significant decrease in the patients' self-management ability, especially in the psychosocial aspect. In our

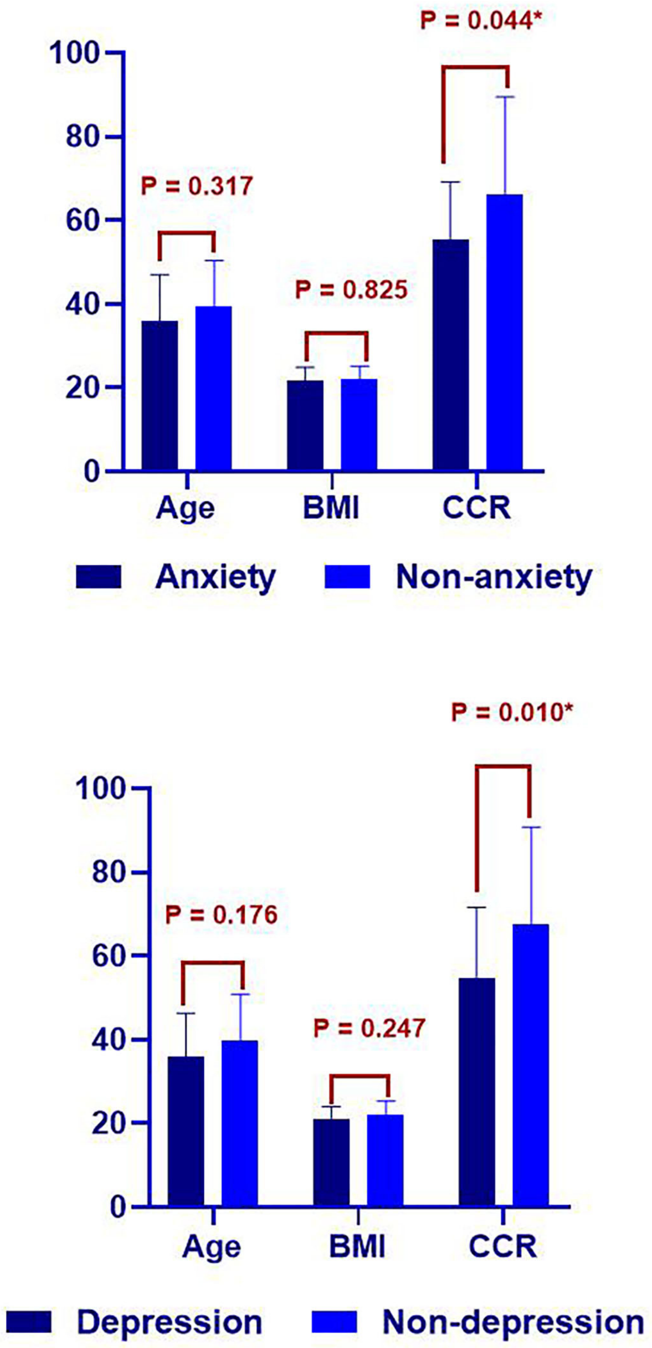

FIGURE 1 | Comparison of age, body mass index (BMI), and creatinine clearance rate (CCR) between the anxiety and non-anxiety groups, and the depression and non-depression groups.

study, 34.1% of the renal transplant recipients had a medium level of self-management, and among the four dimensions of self management, psychosocial management scored the lowest. This finding is consistent with the results of Xie et al. (15). Psychological factors and negative emotions are well-known risk factors of poor quality of life in renal transplant recipients (16). Anxiety can affect the patients' quality of life by influencing their psychological management (11), while depression can lead to a twofold increase in the risk of transplant failure and death (17). As reported previously, self-management plays an important role in preventing the development of chronic diseases, reducing the incidence of complications, and improving the quality of life (18). Moreover, adhering to a good self-management program is an important factor related to graft survival and medium- and

TABLE 5 | Comparison of creatine clearance, self-management ability, and general data between the anxiety and depression groups.

Index	**Anxiety groups**				**Depression groups**			
	Anxiety (*n* = 11)	**Non-anxiety (*n* = 77)**	**Z/X**	***P***	**Depression (*n* = 19)**	**Non-depression (*n* = 69)**	**Z/X**	***P***
Sex (*n*, %)			1.14	0.23			0.65	0.41
Male	9 (81.8)	49 (63.6)			14 (73.7)	44 (63.8)		
Female	2 (18.2)	28 (36.4)			5 (26.3)	25 (36.2)		
DE (*n*, %)			−2.72	<0.01			−2.54	<0.05
Primary school or lower	2 (18.2)	2 (2.5)			2 (9.0)	2 (3.0)		
Junior middle school	5 (45.4)	20 (25.9)			11 (50)	14 (21.2)		
High school or technical secondary school	3 (27.2)	21 (27.2)			4 (18.1)	20 (30.3)		
Junior college or bachelor's degree	1 (9.0)	34 (44.1)			5 (22.7)	30 (45.4)		
Monthly income (*n*, %, yuan)			−2.72	0.06			−1.52	0.12
0–2,000	8 (72.7)	28 (36.3)			13 (59.0)	23 (31.8)		
2,001–4,999	0 (0)	19 (26.4)			2 (9.0)	17 (25.7)		
5,000–7,999	3 (27.2)	22 (28.5)			6 (27.2)	19 (28.70		
≥8,000	0 (0)	8 (10.3)			1 (4.5)	7 (10.6)		
Payment method			6.84	<0.05			2.31	0.31
Medical insurance	8 (72.7)	73 (94.8)			16 (84.2)	65 (94.2)		
At one's own expense	2 (18.2)	2 (2.6)			2 (10.5)	2 (2.9)		
Others	1 (9.1)	2 (2.6)			1 (5.3)	2 (2.9)		
D	28.5 (26.2, 34.5)	30 (28, 34)	−1.11	0.26	30 (26, 34)	30 (28, 34)	−0.48	0.62
T	36 (30.5, 39)	37 (34, 38)	−0.97	0.33	36 (32, 38)	37 (34, 38)	−0.44	0.65
SP	15.5 (13.2, 18.5)	17 (15, 18)	−1.87	0.06	16 (14, 19)	17 (15, 18)	−0.9	0.36
PA	11 (10, 13.2)	12 (11, 14)	−2.7	<0.01	11 (10, 12)	12 (11, 14)	−2.96	<0.01
Total	86.5 (81, 105.7)	98 (88.5, 102)	−1.7	0.08	92.47 ± 11.59	95.59 ± 8.74	−1.1	0.27

DE, degree of education; D, diet management score; T, treatment management score; PS, psychosocial management score; PA, physical activity management score; Total, total score of the self-management scales.

long-term quality of life in renal transplant recipients. However, the correlations of anxiety and depression with patients' self-management ability and CCR have not been well documented.

In this study, we analyzed the general data of patients and the relationships of anxiety and depression with self-management ability and endogenous creatinine clearance. We found that endogenous creatinine clearance was negatively correlated with age and degree of depression and positively correlated with body mass index, treatment management score and psychosocial management score, but it showed no correlation with the degree of anxiety of the patient. In other words, the higher the degree of depression, the lower the endogenous creatinine clearance rate, but the higher the level of self-management in treatment and psychosocial aspects, the higher the endogenous creatinine clearance rate.

We further analyzed the factors affecting the endogenous creatinine clearance rate and found that sex, age, body mass index, treatment management ability, and depression were the main influencing factors of endogenous creatinine clearance, which could explain 33.3% of the total variation. Although age and sex are factors that we cannot modify, we can guide patients to maintain a good body mass index through reasonable diet and exercise, and improve their physical function (19).

Aside from the same influencing factors found in our and previous studies, self-management ability and depression were also independent influencing factors of endogenous creatinine clearance found in this study. The self-management of treatment among renal transplant recipients mainly includes taking drugs according to doctor's advice, getting used to the effects and side effects of the drugs, self-monitoring body temperature, blood pressure, and urine volume, and paying regular revisit to the docyor (20). The level of treatment management ability has a significant impact on the endogenous creatinine clearance rate of patients. Thus, medical staff should pay attention to the cultivation of patients' treatment management ability. It is also very necessary to screen patients for depression to provide a basis for targeted treatment and nursing measures.

Creatinine clearance is the most important index for evaluating renal function. To our knowledge, this study is the first to analyze the correlations of anxiety and depression with self-management and creatinine clearance in renal transplant recipients. We compared the general data, endogenous creatinine clearance rate, and self-management ability of patients with or without anxiety and depression, and found that patients with a higher educational level and health insurance payment support had a lower incidence of anxiety and depression. Patients without anxiety or depression had a higher psychosocial management ability and higher endogenous creatinine clearance. These findings suggests that for patients with a lower level of education, we should adopt health education and communication methods that are easier and more acceptable to them, and strengthen their knowledge and understanding of renal transplantation and self-management. As mentioned by Schmid-Mohler et al. (21), health insurance support would also be necessary for transplant patients. Once again, our results confirmed the significant effect of depression on endogenous creatinine clearance. Thus, it is important to screen renal transplant recipients for anxiety and depression to promote targeted interventions, especially psychosocial interventions. We also found that the incidence of depression was higher than expected; therefore, the management of depression could be considerably significant in improving the CCR of patients. This implies that treatment and nursing interventions alone may not be adequate to solve these psychosocial problems of these patients. A psychological consultation team with knowledge of kidney transplantation is needed (22).

Our study has some limitations. We only investigated renal transplant recipients in one hospital, and the sample size was limited. This setup may not provide a complete picture of the correlations of anxiety and depression with self-management and creatinine clearance in renal transplant recipients. Another limitation is that because *t*-tests were used, potential confounding of age and gender on the association of pyschological factors and clearance cannot be determined. Nevertheless, the findings of this study have an important practical significance because they showed the negative effects of anxiety and depression on self-management, and the negative effects of depression on creatinine clearance. Therefore, we should screen renal transplant recipients for anxiety and depression and comprehensively evaluate factors such as the patient's age, cultural background, socioeconomic status, and family relationships before surgery. A psychological service team with a professional knowledge of transplantation should be established to provide more-comprehensive health management services for transplant patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Affiliated Hospital of Zunyi Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The Role of Socioeconomic Status, Family Resilience, and Social Support in Predicting Psychological Resilience Among Chinese Maintenance Hemodialysis Patients

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Objectives: Evidence regarding the possible influence of social factors on psychological resilience among maintenance hemodialysis patients is scarce. The aim of this study was to explore the relationship among socioeconomic status, family resilience, and social support, and psychological resilience among Chinese maintenance hemodialysis patients.

Methods: This cross-sectional study was conducted in the hemodialysis centers of three comprehensive hospitals in China from September to December 2020 using convenience sampling. Two hundred fifty-eight patients receiving maintenance hemodialysis were investigated using a sociodemographic questionnaire, the Chinese version of the Medical Outcomes Study-Social Support Survey (MOS-SSS), Chinese Family Resilience Assessment Scale (C-FRAS), and Chinese version of the Conner and Davidson resilience scale (CD-RISC).

Results: Maintenance hemodialysis patients reported a low level of physical resilience, with a score of (58.92 ± 15.27). Hierarchical linear regression analysis showed that education level ($\beta = 0.127$, $p = 0.018$), maintenance of a positive outlook by the family ($\beta = 0.269$, $p = 0.001$), positive social interaction support from the family ($\beta = 0.233$, $p = 0.002$), and tangible support ($\beta = -0.135$, $p = 0.037$) were significantly associated with psychological resilience.

Conclusion: SES, family resilience and social support may be potential predictive factors of psychological resilience. Interventions to improve the family resilience and social support may be beneficial to promote the psychological resilience of Chinese maintenance hemodialysis patients.

Keywords: maintenance hemodialysis, social support, family resilience, psychological resilience, socioeconomic status

INTRODUCTION

Hemodialysis is the main form of renal replacement therapy in the terminal stage of chronic renal failure (1). According to the latest census data released in the China Kidney Disease Network Data Report (2), the prevalence of maintenance hemodialysis among patients with chronic renal failure in China is 402.18 per million. Hemodialysis treatment preserves the lives of patients with terminal stage renal failure but does not prevent the emotional suffering associated with chronic stress related to the disease burden, dialysis treatment, functional limitation, and fear of death (3–7). The incidence of emotional distress is higher in patients who received maintenance hemodialysis than in those with chronic kidney disease alone (8). It has been proposed that an individual's internal resources and external support play important roles in overcoming emotional distress during the treatment (9, 10).

Psychological resilience, defined as an individual's ability to actively mobilize all favorable factors to maintain or restore relatively stable mental and physical functions in the face of stressful life events and adversity (11), is widely recognized as an individual's competency and strength to successfully cope with stress (12). Higher psychological resilience is associated with greater acceptance of the disease, higher compliance with therapeutic regimens, and more favorable outcomes in patients with chronic renal diseases (13, 14). Lower psychological resilience is associated with emotional dysregulation (15) and variations in sensory processing (16, 17), which can increase the risk of suicidality in some patient populations (18). As cognitive flexibility is reported to be a critical factor to prevent negative outcomes and suicidal behavior in response to stressful life events (19), it is important to explore the psychological resilience of maintenance hemodialysis patients.

The systematic self-reflection model of resilience highlights the resilience resource of an individual, such as socioeconomic status (SES), family resources, and social support, which is one of the fundamental capacities for psychological resilience. The role of SES in the development of psychological resilience is contradictive. Wister et al. (20) suggests that individuals with higher SES have greater resilience, as they have greater social and economic resources available to them compared to individuals of lower SES. Other theorists (21) hypothesized that individual with low SES will exhibit prolonged, high-effort coping behavior to deal with emotional stress. To our best knowledge, there is no empirical study exploring the relationship of SES and psychological resilience among maintenance hemodialysis patients.

Social support, a multidimensional concept, is defined as the provision of psychological and material resources by caregivers, medical staff, and other social networks to benefit an individual's ability to cope with stress (22). The subjective perception of social support has been identified as a protective factor for psychological resilience in other populations, such as adolescents (23, 24), cancer patients (25, 26), and older individuals (27). However, the role of objective social support on psychological resilience is less clear. Objective social support can come in varying forms, including tangible support, informational/emotional support, positive social interaction support, and affectionate support (28). To better understand the mechanisms underlying the effects of social support, it is vital to understand the types of social support that are beneficial for psychological resilience.

Family resilience, one of the most important family resources, is defined as a family's ability to withstand and rebound from adversity and to become stronger and more resourceful (29). Previous studies have identified multiple dimensions of family resilience, such as family cohesion, family communication, a family's ability to make meaning of adversity, maintaining a positive outlook, utilizing social and economic resources, etc. (30). However, there are few studies exploring the effect of each aspect of family resilience on individual resilience. Only one recent study of Japanese hemodialysis patients found family communication was associated with higher psychological resilience, while family cohesion was not associated with individual resilience (31).

Some scholars caution that the protective or risk characteristic of psychological resilience depends on the context and meaning of each element, particularly how each factor is perceived by an individual (32). Therefore, the purpose of this study is to examine the predictive roles of SES, family resilience, and social support for psychological resilience among Chinese Maintenance hemodialysis patients. We hypothesized that socioeconomic status, family resilience, and social support will be positively associated with psychological resilience after controlling for demographic and clinical variables.

METHODS

Participants

Two hundred eighty patients were recruited using the convenience sampling method in this study. The inclusion criteria were as follows: (1) age 18 years or above; (2) receiving hemodialysis regularly for more than 3 months; (3) no communication barriers; (4) willing to participate in this study. The exclusion criteria were: (1) physician-diagnosed psychiatric or mental disorders based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, TR) (33), such as schizophrenia, bipolar disorder, and depression; (2) neurological disorders or cognitive impairments (e.g. delirium, dementia); and (3) inability to communicate verbally or complete the questionnaires. The investigator carefully collected the participants' psychiatric histories by reviewing their medical records and questioning the patients or their family members. Of the 280 eligible maintenance hemodialysis patients invited to participate, 22 eligible participants declined to participate due to a lack of interest or fatigue. The remaining 258 participants all returned complete and valid questionnaires, resulting in a valid sample size of 258 (participation rate = 92.14%).

Procedure

After obtaining ethical approval for the study from the Affiliated Hospital of the Medical University Ethics Committee (No. 2020198), this cross-sectional study was conducted in accordance with the Declaration of Helsinki in the hemodialysis center of three comprehensive hospitals in Zhejiang Province, China, from September to December 2020. Data were collected using structured questionnaires with the cooperation of hemodialysis center nurses. A trained investigator identified potential eligible patients by reviewing their medical records and asking about their psychiatric history for initial screening. The eligible participants were informed of the purpose and procedure of the study. Written informed consent was obtained from all participants before starting any procedures, and the confidentiality of their information was guaranteed. The participants were instructed to complete the pen-and-paper self-reported questionnaires in a quiet room before the hemodialysis treatment. For participants who could not write, the investigator read out the questionnaire items verbatim without adding further explanation and completed the questionnaires according to the patient's responses. The entire survey process lasted for 20–30 min, and the investigator immediately reviewed the questionnaires and asked the patients to provide any missing items after each survey was completed. All participants were provided with a small gift of a cookie valued at $1 as compensation.

Measures

Demographic and Clinical Variables

The following variables were assessed: age, gender, employment status, marital status, medical insurance (yes/no), disease duration, dialysis duration, and frequency of hemodialysis and comorbidities.

SES

Two indicators for SES were assessed. Financial status was measured as the monthly household income per capita and was coded into four categories, from 1 (<2,000 RMB) to 4 (>6,000 RMB). Education was measured as the highest grade of schooling completed and was coded into four categories, from 1 (primary school) to 4 (college or higher).

Social Support

The Chinese version of the Medical Outcomes Study–Social Support Survey (MOS-SSS) (34), a 19-item scale, was used to assess the extent to which each individual had the support of others to cope with their stressful situation during the course of chronic disease. MOS-SSS recognizes the following four types of social support: informational/emotional support (eight items, expression of positive effect and empathetic understanding/offering of advice, information, guidance or feedback), tangible support (four items, provision of material aid or behavioral assistance), positive social interactive support (four items, the availability of other persons to entertain the patient), and affectionate support (three items, expressions of love and affection). Participants are asked to indicate how often each type of social support is available to them when they need it. A 5-point response ranging from 1 = none of the time to 5 = all of the time is used. The total score ranges from 19 to 95, with higher scores indicating higher levels of social support. The Cronbach's α coefficient was 0.944 for the total score in the present study.

Family Resilience

Family resilience was measured using the 44-item Chinese version of the Family Resilience Assessment Scale (C-FRAS) (30), which comprises four subscales: family communication and problem solving (27 items), utilizing social and economic resources (eight items), maintaining a positive outlook (six items), and ability to make meaning of adversity (three items). Each item is rated on a four-point Likert scale from 1 = strongly disagree to 4 = strongly agree, with total scores ranging from 44 to 176. Higher scores indicate higher levels of family resilience. The Cronbach's α coefficient was 0.968 for the total score in the present study.

Psychological Resilience

Psychological resilience was assessed using the Chinese version of the Conner and Davidson resilience scale (CD-RISC) (35). The 25-item CD-RISC contains three subscales, namely tenacity (13 items), strength (eight items), and optimism (four items). It uses a Likert five-point scale from 0 = not true at all to 4 = true all the time, with a total score of 0–100. Higher scores indicate higher levels of psychological resilience. The Cronbach's α coefficient of the scale in the present study was 0.927.

Statistical Analysis

All statistical analysis was performed using IBM SPSS 25.0 (IBM Corp., Armonk, NY, USA). The *t*-test or one-way ANOVA was used to compare the groups. Pearson's *r* correlations were calculated to test for unadjusted associations between SES, social support, family resilience, and psychological resilience.

As the total scores of psychological resilience approached normality ($W = 0.995$, $p = 0.479$), hierarchical linear regression analyses were conducted with the sociodemographic and clinical variables in Step 1. SES was added in Step 2, family resilience was included in Step 3, and social support was entered in Step 4. Statistical significance was set at the level of 0.05 or less (two-tailed). Statistical significance was interpreted as a $p < 0.05$ (two-tailed).

RESULTS

Descriptive Statistics

Two hundred fifty-eight maintenance hemodialysis patients (174 men and 84 women), with a mean age of 57.6 ± 13.83 years, submitted complete questionnaires. Participants were predominantly unemployed ($n = 213$, 82.6%), married/cohabitating ($n = 228$, 88.4%), with medical insurance ($n = 253$, 98.1%), and diagnosed with chronic renal failure for no <10 years ($n = 137$, 53.1%). Regarding the duration of hemodialysis, 48 (18.6%) participants had been treated for <1 year, 109 (42.2%) for 1–5 years (not including 5 years), 65 (25.2%) for 5–10 years (not including 10 years), and 36 (14%) for no <10 years. The mean duration of maintenance hemodialysis treatment was 58.38 months (SD = 48.33, range 4–236).

Regarding the SES, the sample comprised participants with education levels of primary school or below ($n = 70$, 27.1%), middle school ($n = 97$, 37.6%), high school ($n = 59$, 22.9%), and college or higher ($n = 32$, 12.4%). For financial status, 38 (14.7%)

participants reported a family monthly income of <2,000 RMB, 93 (36.0%) reported a family monthly income of 2,000–4,000 RMB, 76 (29.5%) reported a family monthly income of 4,001–6,000 RMB, and 51 (19.8%) reported a family monthly income of >6,000 RMB. The characteristics of the study population are summarized in **Table 1**.

Association Between Demographic and Clinical Variables, SES, and Psychological Resilience

A significant difference in psychological resilience was found according to different demographic variables including age ($t = 2.027$, $p = 0.044$), occupational status ($t = 3.890$, $p < 0.001$), and marital status ($t = -2.122$, $p = 0.035$). A significant difference was also observed in the psychological resilience of patients with different educational levels ($F = 11.379$, $p < 0.001$) and different monthly household incomes per capita ($F = 9.667$, $p < 0.001$; see **Table 1**).

Correlation Between Social Support, Family Resilience, and Psychological Resilience

The results of the correlation analysis are shown in **Table 2**. Significant correlations were observed between all four domains of social support and psychological resilience ($r = 0.207$–0.543, $p < 0.01$). The family resilience subscales also positively correlated with psychological resilience ($r = 0.390$–0.575, $p < 0.01$).

Hierarchical Linear Regression Analysis

Hierarchical linear regression analysis was conducted to identify the relative contribution of the independent variables to psychological resilience (see **Table 3**). Variables correlated with psychological resilience in the univariate analyses were entered into the model. When the demographic characteristics were controlled in Step 1, SES, which was tested in Step 2, explained an additional 12.8% of variance in psychological resilience. Participants with higher levels of education ($\beta = 0.286$, $p < 0.001$) and monthly household income per capita ($\beta = 0.151$, $p = 0.014$) reported greater levels of psychological resilience. Family resilience, which was included in Step 3, explained 23.3% of the variance in psychological resilience. Higher scores in the maintenance of a positive outlook ($\beta = 0.325$, $p < 0.001$) were indicative of greater levels of psychological resilience. After controlling for the demographics, SES, and family resilience, tangible support ($\beta = -0.135$, $p = 0.037$) and positive social interaction support ($\beta = 0.233$, $p = 0.002$) emerged as significant predictors of psychological resilience. The addition of social support in Step 4 accounted for 5.5% incremental criterion variance. Furthermore, as shown in **Table 3**, monthly household income per capita no longer showed predictive utility in the last step ($\beta = 0.096$, $p = 0.058$).

DISCUSSION

In the present study, maintenance hemodialysis patients reported a low level of psychological resilience (58.92 ± 15.27), which was significantly lower than the normal level in the general population in China (65.46 ± 13.93) (36), but was similar to the level of Chinese cancer patients (57.12 ± 13.56) (37). The treatment process and severe lifestyle changes related to maintenance hemodialysis may reduce the ability of patients to adapt and cope with adversity (38). Since the low psychological resilience of hemodialysis patients is associated with their lower health-promoting behavior and higher level of depression (8), it is highly important for clinical staff to help these patients increase their psychological resilience.

As hypothesized, the results of this study indicated that better SES (higher education level and family income) contributed to a higher level of psychological resilience in maintenance hemodialysis patients, which supports the theory proposed by Wister et al. (20). Maintenance hemodialysis patients with better SES might have more comprehensive understanding of the disease, adopt more effective problem-solving strategies, and have access to more information/health care services (39, 40). Interestingly, the predictive utility of family monthly income was no longer significant when social support was included in the model, which indicates that the family financial level of maintenance hemodialysis patients may affect the psychological resilience through the role of social support. Therefore, it will be more important in future studies to develop more appropriate social support systems for maintenance hemodialysis patients with low SES.

Our results support the hypothesis that family resilience is positively correlated with psychological resilience, indicating that having a family that flexibly responds to changes in a highly challenging environment may lead to positive changes in mental health among hemodialysis patients (41). Maintaining a positive outlook was an independent family resilience factor that influenced psychological resilience in this study, which suggests that maintaining a positive outlook is the most fundamental element of family resilience to foster an individual's psychological resilience (42). Our findings provide some new evidence that a family's shared belief in maintaining a positive outlook is essential to mobilize relational resources to support the positive adaptation of the family and, thus, to guide family members to embrace hope and flexibly respond to hardship when faced with stressful events. Therefore, it is important for families to preserve and nourish their shared beliefs and positive outlook as a way to promote psychological resilience during the process of disease and hemodialysis treatment.

Our findings also support the hypothesis of a positive correlation between social support and psychological resilience. Social interaction support showed a positively predictive effect on psychological resilience, possibly due to the fact that individuals who reported greater support received in positive social interactions would have higher levels of self-efficacy (43) and more resources to cope with stress and the burden of illness (44). Qualitative studies found that positive social interactions gives hemodialysis patients a sense of meaning in life and hope for the future (45), as well as positive emotional experiences and self-worth (46). Thus, nursing interventions focused on promoting positive social interaction

TABLE 1 | Psychological resilience in relation to demographic, clinical, and SES characteristics (*N* = 258).

Variable	***N* (%)**	**Psychological resilience (Mean ± SD)**	***t/F***	***p***
Demographic and clinical variables				
Age			2.027	0.044
<60 years	130 (50.4%)	60.82 ± 15.54		
≥60 years	128 (49.6%)	56.99 ± 14.80		
Gender			1.355	0.177
Male	174 (67.4%)	59.82 ± 15.27		
Female	84 (32.6%)	57.07 ± 15.18		
Employment status			3.890	<0.001
Employed	45 (17.4%)	66.76 ± 13.99		
Unemployed	213 (82.6%)	57.27 ± 15.04		
Marital status			−2.122	0.035
Single/divorced/widow/separated	30 (11.6%)	53.40 ± 12.44		
Married/cohabitating	228 (88.4%)	59.65 ± 15.48		
Medical insurance				
Yes	253 (98.1%)	59.12 ± 15.25	−1.471	0.143
No	5 (1.9%)	49.00 ± 14.09		
Duration of disease			0.442	0.723
<1 year	13 (5.0%)	58.46 ± 16.78		
1–<5 years	53 (20.5%)	60.98 ± 15.28		
5–<10 years	55 (21.3%)	57.78 ± 16.23		
≥10 years	137 (53.1%)	58.63 ± 14.82		
Duration of hemodialysis			1.930	0.125
<1 year	48 (18.6%)	58.48 ± 16.03		
1–<5 years	109 (42.2%)	61.44 ± 15.46		
5–<10 years	65 (25.2%)	56.37 ± 15.15		
≥10 years	36 (14.0%)	56.50 ± 13.08		
Comorbidities			0.377	0.686
No	77 (29.8%)	58.22 ± 17.00		
One	119 (46.1%)	59.82 ± 13.85		
Two or more	62 (24.0%)	58.08 ± 15.76		
SES variables				
Education level			11.379	<0.001
Primary School and below	70 (27.1%)	52.29 ± 13.54		
Middle School	97 (37.6%)	58.01 ± 14.73		
High School/secondary school	59 (22.9%)	63.15 ± 13.40		
College or higher	32 (12.4%)	68.41 ± 16.97		
Monthly household income per capita			9.667	<0.001
<2,000 RMB	38 (14.7%)	51.74 ± 14.01		
2,000–4,000 RMB	93 (36.0%)	57.75 ± 14.78		
4,001–6,000 RMB	76 (29.5%)	58.01 ± 13.95		
>6,000 RMB	51 (19.8%)	67.76 ± 15.37		

support as appropriate and directly or indirectly mobilizing or expanding the social network of the patient may be an effective strategy to improve the psychological resilience of patients. In contrast to our hypothesis, tangible support was negatively predictive of psychological resilience after controlling for other kinds of social support in this study. High tangible support with activities for daily living may threaten self-esteem and the sense of competence and mastery (47). Patients who perceived high tangible support without affectionate supportive communication may view such favors as expressions of obligation rather than a manifestation of love, thereby reducing psychological resilience (48). Therefore, it is important for nurses and caregivers to strike a balance between providing help and maintaining the patient's sense of self-esteem and self-worth, despite the patient's reliance on others for care and support (49).

TABLE 2 | Correlation analysis between social support, family resilience, and psychological resilience ($N = 258$).

	Mean ± SD	1	2	3	4	5	6	7	8	9	10	11
1. Tangible support	16.74 ± 3.40											
2. Informational/emotional support	24.85 ± 6.05	0.554**										
3. Positive social interaction support	12.71 ± 3.37	0.465**	0.767**									
4. Affectionate support	11.26 ± 2.40	0.688**	0.749**	0.644**								
5. FCPS	81.79 ± 7.85	0.308**	0.496**	0.443**	0.459**							
6. USER	21.89 ± 2.58	0.165**	0.343**	0.316**	0.216**	0.630**						
7. MPO	17.74 ± 2.12	0.276**	0.467**	0.439**	0.425**	0.825**	0.560**					
8. AMMA	9.03 ± 0.89	0.308**	0.432**	0.393**	0.370**	0.790**	0.565**	0.609**				
9. Tenacity	29.61 ± 8.41	0.141*	0.450**	0.484**	0.359**	0.531**	0.373**	0.545**	0.400**			
10. Strength	20.42 ± 5.23	0.209**	0.484**	0.540**	0.403**	0.519**	0.354**	0.557**	0.373**	0.892**		
11. Optimism	8.89 ± 2.67	0.331**	0.539**	0.526**	0.455**	0.480**	0.362**	0.482**	0.439**	0.677**	0.682**	
12. Psychological resilience	58.92 ± 15.27	0.207**	0.508**	0.543**	0.415**	0.554**	0.390**	0.575**	0.425**	0.975**	0.953**	0.781**

FCPS, Family Communication and Problem Solving; USER, Utilizing Social and Economic Resources; MPO, Maintaining a Positive Outlook; AMMA, Ability to Make Meaning of Adversity; *$p < 0.05$, **$p < 0.01$.

TABLE 3 | Hierarchical regression analysis of factors influencing psychological resilience.

Variables	**Model 1**		**Model 2**		**Model 3**		**Model 4**	
	β	**SE**	β	**SE**	β	**SE**	β	**SE**
Demographic variables								
Age	−0.104	1.970	−0.063	1.890	−0.090	1.609	−0.061	1.564
Employment status	−0.233*	2.533	−0.178*	2.394	−0.120*	2.304	−0.071	1.989
Marital status	0.194*	2.952	0.221*	2.793	0.181*	2.385	0.134*	2.454
SES								
Education level			0.286*	0.987	0.179*	0.858	0.127*	0.836
Monthly household income per capita			0.151*	0.966	0.104*	0.825	0.096	0.790
Family resilience								
FCPS					0.171	0.219	0.142	0.212
USER					0.058	0.366	0.043	0.357
MPO					0.325*	0.618	0.269*	0.599
AMMA					−0.011	1.367	−0.030	1.322
Social support								
Tangible support							−0.135*	0.289
Informational/emotional support							0.087	0.214
Positive social interaction support							0.233*	0.331
Affectionate support							0.037	0.531
F	8.753		14.336		22.982		19.486	
R^2	0.094		0.221		0.455		0.509	
Adjusted R^2	0.083		0.206		0.435		0.483	
R^2-change	0.094		0.128		0.233		0.055	

β, Standardized estimate; FCPS, Family Communication and Problem Solving; USER, Utilizing Social and Economic Resources; MPO, Maintaining a Positive Outlook; AMMA, Ability to Make Meaning of Adversity.

Implications for Practice

From a clinical perspective, this study highlights the practical importance of assessing the SES, family resilience, and social support to screen patients with a risk of low psychological resilience, and provides evidence for tailoring family resilience and social support-oriented intervention to improve the psychological resilience of maintenance hemodialysis patients. Specifically, clinical practitioners can conduct family interventions that focus on promoting the shared family belief of a positive outlook toward the disease and treatment to foster individual resilience. Clinical practitioners should also evaluate the sources of social support during treatment and provide appropriate help to guide maintenance hemodialysis patients to seek effective support and enhance their resilience.

Limitations

There are several limitations of the present study. First, causal relationships cannot be inferred due to the cross-sectional design of this study. Therefore, longitudinal study designs should be used to further explore the complicated dynamic effect of SES, family resilience, and social support on psychological resilience. Secondly, the subjective nature of self-reported questionnaires can lead to reporting bias, especially since psychiatric pathologies and psychological disorders in the participants were not evaluated through specific and structured interviews. However, we initially reviewed the medical records and inquired about the psychiatric history of the patients. Thirdly, family SES was measured only based on the family income and education level in this study. Multiple indices of family SES should be used in future studies. Fourthly, although we adjusted for demographic factors in the analysis, there may be residual confounding factors present, such as the mood of the day and comorbidities. Finally, the generalizability of the results of this study may be limited by convenience sampling. It is necessary to conduct multi-center investigations in future studies.

CONCLUSION

Our study showed a low level of psychological resilience among Chinese maintenance hemodialysis patients. The present study demonstrated that SES, represented by education level and family income, is an important predictor of psychological resilience. Maintaining a positive outlook as the most important aspect of family resilience and positive social interactive support positively predicted the patient's level of psychological resilience, while tangible support served as a negative predictor of psychological resilience. Therefore, an approach that focuses on psychological resilience, which patients with lower SES can apply to deal with stress, may reduce the health disparity. In addition, family interventions tailored to maintaining the family's positive outlook or interventions that promote appropriate social support are needed to improve the psychological resilience of maintenance hemodialysis patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Wenzhou Medical University Ethics Committee (No. 2020198). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YQ: data collection, writing-original draft, writing review, and editing. YH, YW, LR, and HJ: data collection, data curation, writing review, and editing. LZ: conceptualization, writing review, and editing. CD: conceptualization, writing-original draft, writing review, and editing. All listed authors meet the authorship criteria and that all authors are in agreement with the content of the manuscript.

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Validation of Death and Dying Distress Scale-Chinese Version and Prevalence of Death Anxiety Among Patients With Advanced Cancer

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Purpose: Death anxiety is commonly experienced by individuals with advanced cancer who have a limited life expectancy. The Death and Dying Distress Scale (DADDS) is a validated measure that was created to capture this experience; but no Chinese version is available to date. We conducted a cross-sectional study to explore the psychometric properties of a Chinese version DADDS (DADDS-C) and address prevalence of death anxiety among patients with advanced cancer.

Methods: Patients with advanced cancer were recruited from Peking University Cancer Hospital. Measures administered included: DADDS-C, Patient Health Questionnaire (PHQ-9), General Anxiety Disorder-7(GAD-7), Quality of Life at End of Life in Cancer (QUAL-EC), Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale (FACIT-sp). McDonald's Omega, Cronbach's alpha, Exploratory Factor Analysis and Confirmatory Factor Analysis were used to test DADDS-C's reliability and validity. Logistic regression analysis was used to identify risk factors for death anxiety.

Results: Of 300 patients approached, 256 (85%) provided informed consent and completed the questionnaires. Of these participants, 43 (16.8%) had moderate death anxiety based on scores of $\geq$45 on the DADDS-C. Three factors (feeling shortness of time, dying and death distress, being a burden to others) explained 71.643% of shared variation with factor loadings ranging from 0.629 to 0.822. Cronbach's alpha was 0.939; Omega total was 0.959. DADDS-C had acceptable convergent and discriminant validity. Logistic regression analysis indicated that two factors (better relationship with healthcare providers and preparation for end of life) protected patients from death anxiety.

Conclusion: DADDS-C is a valid tool for measuring death anxiety in Chinese patients with advanced cancer. The presence of at least moderate death anxiety in a substantial minority of these patients calls for screening for this symptom and for more routine psychological interventions to alleviate and prevent such distress in this population.

Keywords: oncology, death anxiety, death and dying distress scale, advanced cancer patients, validation, palliative care, psychology, psychometrics

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INTRODUCTION

Cancer is still one of the leading causes of death in China, with almost four million new cancer cases in 2015 and more than 2 million cancer deaths (1). Although the 5-year survival rate for of all kinds of cancer in the world has improved in recent years, that for most cancer types in China is still lower than in developed countries (2, 3). Further, the symptom burden of those living with advanced cancer is substantial (4–6), with moderate to severe symptoms of depression and demoralization reported in almost one quarter of such individuals (7, 8) and more than 40% reporting moderate to severe symptoms of death anxiety (9). Sussman had defined death anxiety as 'psychological distress in the form of anxiety about one's death that contributes to functional impairment in one's life' (10). Though some of patients with death anxiety didn't meet all criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-anxiety disorder, this group of patients might have poorer death quality (11). Terror management theory (TMT) suggested that death anxiety is a fundamental human fear that is amplified by mortality salience (awareness that one's death is inevitable), different from general anxiety which is triggered by excessive worry about practical problems in daily life (12). Based on this theory, self-esteem (experiencing sense of meaning and value) was the core protective factor for death anxiety and was suggested to be integrated into death anxiety management (13).

Talking about death and dying is taboo in many cultural systems, which makes it difficult for it to be openly discussed and studied in many settings (14, 15). It is common in this circumstance to see patients, families and medical staff be aware of the imminence of death and dying but to never discuss it openly (16). This taboo on open discussion among Chinese people is evident in the Confucian concept of 'highlighting birth and avoiding death' (17). Confucian ideology have deeply influenced Chinese culture, which is a background for Chinese patients' outlook on life. Benevolence, righteousness, courtesy, wisdom and trust are five core ideas, which has resulted in respecting the elderly and caring more for family development than individuals, as said by Confucius: to subdue Oneself and Return to the Proprieties is Perfect Virtue (18). This ideology also has influenced individuals' thinking about death and dying.

Death anxiety has been shown to be common in patients with advanced cancer and associated with other psychological disturbances. At least moderate death anxiety has been reported by 32% of a mixed sample of patients with advanced cancer (19) and in 43% of patients with non-small cell metastatic lung cancer (9). Death anxiety in these and other studies has been associated with depression, demoralization, fear of disease progression and with less attachment security (9, 20–24).

Some measures of death anxiety have been validated in Chinese (25, 26), but none has been specifically designed for patients with advanced cancer. Yang reported on the use of a Chinese version of Templer's Death Anxiety Scale (DAS) for colorectal cancer patients, but no other studies using this tool in China have been reported. Some items on the DAS are not tailored for individuals with advanced cancer, such as item 11 "I am really scared of having a heart attack," and item 13 "I shudder when I hear people talking about a world war III" (26).

The Death and Dying Distress Scale (DADDS) was developed and validated by a clinical research team at Princess Margaret Cancer Center in Toronto, to assess distress about dying and death in individuals with advanced cancer (27, 28) and has been validated in German (21). The advantages for this scale were as below: (1) it was designed specifically for cancer patients and practical for further interventional researches among this population; (2) all items focused on death and dying distress and no specific scenarios, which was beneficial for generalizing utilization among patients with limited life. Recent research demonstrated that the DADDS has two subfactors, which are Finitude, referring to distress about the perceived shortness of time, and Dying, which refers to distress about the process of dying and death (29).

The present cross-sectional study is a preliminary examination of the validity of the Death and Dying Distress Scale-Chinese version (DADDS-C) in patients with advanced cancer. It was conducted in preparation for a randomized controlled trial (RCT) of Managing Cancer and Living Meaningfully (CALM) therapy in Chinese patients with advanced cancer "(ID: ChisCRT1900023129)." We hypothesized that DADDS-C would be a valid measurement for death anxiety with two factors as the former researchers suggested (item 1–10 for factor 1-Finitude, item 11–15 for factor 2-Dying) (29), could be used for death anxiety assessment, and death anxiety would be positively associated with anxiety, depression, lower quality of life and negatively associated with spiritual well-being. This cross-sectional study was designed to: (1) test the structure and validation of DADDS-C locally with factor analyses; (2) addressing psychometric priority about this measurement; (3) explore the prevalence and independent risk factors of death anxiety among Chinese patients with advanced cancer through multiple regression analysis.

MATERIALS AND METHODS

Participants and Procedure

This cross-sectional study was approved by Peking University Cancer Hospital Ethics Committee (No. 2018YJZ24) on 25 May, 2018. Participants were a convenience sample of inpatients and outpatients with advanced cancer recruited from Peking University Cancer Hospital from June, 2018 to December, 2018, and the patients were approached both from oncology wards and psycho-oncology clinic. We trained study coordinators and checked their competence of evaluation consistency for delivering all measurements in this study. Inclusion criteria for participants were: (1) age ≥18 years old; (2) pathology diagnosis of advanced cancer [Union for International Cancer Control-UICC TNM classification of Malignant Tumor, stage III and stage IV (30)]; (3) expected survival time ≥6 months; (4) being able to provide informed consent; (5) education level ≥ primary school or the ability to understand the questionnaires. Patients with moderate to severe cognitive dysfunction (according to psychiatrists' interview before registered) and those receiving psychosocial intervention or anti-psychotic treatments were excluded. Most participants answered questionnaires fluently by themselves; some of them were assisted by study coordinators. All 256 participants were attached for repeat assessment by phone 7–14 day after the initial completion, but only 27 patients finished the re-test; no demographic difference was found between this 27 group and the other patients who rejected re-test. The re-test was rejected mostly by patients' family members, because they thought the items in DADDS-C would trigger patients' negative emotion. Sufficient data were therefore not available to determine test-retest reliability.

Translation of DADDS-C

We completed the translation according to the 5 steps of World Health Organization (WHO) translation methodology (31). In collaboration with the developers of the DADDS at the Princess Margaret Cancer Center, a bilingual team of experienced psychologists and psychiatrists (more than 3-years' experience of being an interpreter and translator on psycho-oncology) translated it into simplified Chinese, which was the authority language and commonly used by majority population in Mainland China. One oncologist professor with language proficiency only in Chinese completed the first translated simplified Chinese version and made some comments. The bilingual team considered these comments and revised the documents, then back-translated into English. The accuracy of the back-translation was confirmed with the team at the Princess Margaret Cancer Center. We conducted pilot testing of DADDS-C with 10 outpatients and their family members; one patient's family member refused to allow the patient to complete the questionnaire, and the other 9 patients and family members provided ratings for all items. No negative feedback was provided by them.

Measures

Demographic and clinical information included: age, sex, religion, marital status, education level, residential status, average family income, medical insurance coverage, diagnosis, and ongoing therapies.

The DADDS is a 15 item self-report scale of distress about death and dying, which has been validated in both English and in German (21, 29). Items are rated on a 6-point Likert scale (0 = I did not experience this thought or concern; 1 = I experienced very little distress; 2 = I experience mild distress; 3 = I experienced moderate distress; 4 = I experienced great distress; 5 = I experienced extreme distress). We retained all 15 items and each item was rated on 6-point Likert scales in DADDS-C. Total scores ranged from 0 to 75. As suggested by Neel (19), a cutoff point of 45 was used to define death anxiety as a dichotomous variable (0 = none to mild distress; 1 = moderate to extreme distress).

The Patient Health Questionnaire (PHQ-9) is a 9-item scale for assessing depression among patients, with total score ranges from 0 to 27. It has been validated in Chinese population, with the Cronbach's is 0.89 and the cutoff point of $\geq$10 was used to define moderate depression (32).

Anxiety was assessed by General Anxiety Disorder-7 (GAD-7), a widely used self-reported scale for anxiety, which has been validated in Chinese general hospital outpatients, with the Cronbach's is 0.898 (33). Total scores range from 0 to 27, with $\geq$10 used as the cutoff for clinical cases of anxiety (33).

Quality of Life at the End of Life-Cancer (QUAL-EC) validated by Lo et al. (34), is a short version of QUAL-E developed by Steinhauser et al. (35). QUAL-EC contains 17 items (1–5 point scale), with subscales of: (1) symptom burden (range score 3–15), with lower score reflecting better outcome; (2) relationship with healthcare provider (range score 5–25), with higher score reflecting better outcome; (3) preparation for end-of-life (range score 4–20), reverse-scored, with lower scores reflecting better outcome; (4) life completion (range score 5–25), with higher scores reflecting better outcome. Subscale scores were used for statistical analysis. The Cronbach's for the subscales were: 0.83 for Symptom Burden, 0.73 for preparation for End-of-Life, 0.83 for Life Completion and 0.80 for Relationship with Healthcare Provider. We translated the QUAL-EC into simplified Chinese by the same translation method as described above for the DADDS-C.

We obtained the simplified Chinese version of the Functional Assessment of Chronic Illness Therapy-Spiritual Well-being (FACIT-sp) from the official website (36) and received a license to use it. This questionnaire has been validated in Chinese cancer patients, with the Cronbach's for subscales ranges from 0.711 to 0.920 (37). This simplified Chinese version of FACIT-sp has 12 items, 5-point Likert scale for items (0–4), two items (4 and 8) should be reverse-scored. It contains two subscales: meaning/peace and faith. Total score was calculated based on the official FACIT-Sp scoring instruction.

Statistical Analysis

Data from questionnaires with more than half of the items missing were not included in the analyses. The demographic and medical information were summarized descriptively in **Table 1**. One-way ANOVA (if homogeneity of variance assumption was satisfied) and non-parametric Kruskal-Wallis H test (if homogeneity of variance assumption was not satisfied) were used to compare DADDS-C scores among demographic and medical characteristics. The results determined which demographic and medical characteristics would be fully considered to enter the logistics regression.

Validation test: Exploratory factor analysis (EFA) (Principal Component Analysis for extraction; Eigenvalue >1) was used to explore the underlying factors for DADDS-C using one-half sample ($N = 128$); Kaiser-Meyer-Olkin Measure and Bartlett's test were used to verify whether EFA could well-conducted. Three methods including Scree Plot (SP) (Eigenvalues >1), Parallel Analysis (PA), and Minimum Average Partial (MAP) were used to corroborate factors number (38). Confirmatory factor analysis (CFA) was used to test which one in two models of DADDS-C (one model was derived from EFA, the other model was suggestion by former research) was preferred using the other half sample ($N = 128$); the cut-off values of CFA indexes used to evaluate model fit were as follows (39): Chi-square/df ration ($\chi 2/\text{df}$) $\leq$2.0, standardized root mean square residual (SRMR) <0.08, root mean square error of approximation (RMSEA) $\leq$0.06, comparative fit index (CFI) $\geq$0.95, Tucker-Lewis index

TABLE 1 | Social demographic and medical information, discrepancy of DADDS among different groups.

Subject	N (%)/M ± SD ($N = 256$)	DADDS, M ± SD	χ^2 or F-value	P-value
Age (y)	50.73 ± 11.35		$\chi^2 = 28.859$	<0.001**
≤44	76 (29.7)	31.59 ± 21.962		
45–59	118 (46.1)	20.77 ± 17.325		
≥60	62 (24.2)	12.69 ± 10.826		
Sex			$F = 0.591$	0.443
Male	30 (11.7)	19.539 ± 17.544		
Female	226 (88.3)	22.369 ± 19.072		
Religious			$F = 0.749$	0.388
Yes	43 (16.8)	24.30 ± 20.085		
No	213 (83.2)	21.57 ± 18.654		
Marital status			$F = 0.198$	0.657
Without partner (single, separated, divorced, widowed)	26 (10.2)	20.46 ± 16.258		
With spouse	230 (89.8)	22.20 ± 19.187		
Education Level			$\chi^2 = 14.456$	0.006**
Primary school and lower	23 (9.0)	10.87 ± 10.047		
Junior middle school	62 (24.2)	21.23 ± 18.104		
High middle school	66 (25.8)	22.52 ± 19.480		
Junior college	41 (16.0)	19.93 ± 17.893		
Undergraduate and above	64 (25.0)	27.66 ± 20.381		
Residential			$\chi^2 = 2.340$	0.126
City	213 (83.2)			
Village	42 (16.4)			
Null	1 (0.4)			
Average family income			$F = 1.877$	0.155
<3,000 Yuan/month	53 (20.7)	20.83 ± 18.903		
3,000–5,000 Yuan/month	90 (35.2)	19.71 ± 17.797		
>5,000 Yuan/month	112 (43.8)	24.65 ± 19.543		
Null	1 (0.4)			
Medical coverage			$F = 3.247$	0.073
Public expense/insurance	91 (35.5)	24.88 ± 19.580		
Self-pay	165 (64.5)	20.45 ± 18.368		
Diagnosis			$F = 0.401$	0.753
Breast	186 (72.7)	21.26 ± 18.259		
Lung	20 (7.8)	24.65 ± 21.313		
Gastrointestinal	26 (10.2)	24.50 ± 19.014		
Others	24 (9.4)	23.08 ± 18.889		
Therapies (surgery, chemotherapy, radiotherapy)			$\chi^2 = 4.316$	0.229
None	44 (17.2)	21.18 ± 20.676		
Surgery, surgery and chemotherapy, surgery and radiotherapy	63 (24.6)	18.46 ± 15.583		
Chemotherapy, radiotherapy, chemotherapy and radiotherapy	57 (22.3)	26.37 ± 21.690		
Surgery and chemotherapy and radiotherapy	92 (35.9)	22.18 ± 18.889		
DADDS-C	22.03 (18.889)			
DADDS-C < 45	43 (16.8)			
DADDS-C ≥ 45	213 (83.2)			
PHQ-9	7.13 (5.510)			
PHQ-9 < 10	189 (73.8)			
PHQ-9 ≥ 10	67 (26.2)			
Suicide Ideation	64 (25.0)			
GAD-7	4.64 (4.953)			
GAD-7 < 10	211 (82.4)			

(Continued)

TABLE 1 | Continued

Subject	N (%)/M ± SD ($N = 256$)	DADDS, M ± SD	χ^2 or F-value	P-value
GAD-7 ≥ 10	45 (17.6)			
FACIT-sp	25.95 (8.445)			
QUAL-EC symptom burden	10.07 (3.204)			
QUAL-EC relationship with health care provider	19.90 (4.078)			
QUAL-EC preparation for end-of-life	12.86 (4.061)			
QUAL-EC life completion	20.75 (4.375)			

$^{**}p < 0.01$.

(TLI) ≥0.95. Cronbach's alpha and McDonald's omega were used for internal consistency reliability. Spearman correlation test was used to explore relationship between DADDS-C total score with other variables (two tails test, with $p < 0.05$) to corroborate the criterion validity of DADDS-C.

Prevalence of death anxiety: descriptive analysis and binary logistic regression (Univariate and Multivariate Regression) were used to explore prevalence and significant risk factors for death anxiety.

Most data analyses were performed using SPSS 25.0 (IBM Corporation), except that McDonald's omega was conducted by R Studio (version 1.3.1093) and CFA was conducted by the SPSSAU project (2020) [Online Application Software], retrieved from http://www.spssau.com.

RESULTS

Demographic and Medical Information

Three hundred patients approached by the study coordinators completed questionnaires. Two hundred and fifty-six valid data (i.e., rating of > 50% of items of all measures) entered into the database for analysis (85.3% validity ratio). The mean age of participants was 50.73 ± 11.35, with most being female, with breast cancer, having no religion, living in cities with spouse, having education level of high middle school and above, and paying for medical costs by themselves (**Table 1**).

Descriptive Statistical Results of Questionnaires

The mean scores of the DADDS-C, PHQ-9, GAD-7, FACIT-sp, four subscales of QUAL-EC and the percentage of patients with moderate and severe death anxiety, depression, general anxiety, suicide ideation are all listed in **Table 1**. The Skewness and Kurtosis of DADDS-C were 0.922 and −0.063. The 6 most frequent symptoms reported on the QUAL-EC in descending order were: pain, fatigue, insomnia, nausea and vomiting, shortness of breath, and anxiety. The three most frequent items reported as the cause of distress on DADDS-C in descending order were: being a burden to others (2.78 ± 1.945), the impact of my death on my loved ones (2.60 ± 1.934), dying and death happening with a lot of pain or suffering (2.27 ± 2.018). Results of One-way ANOVA or non-parametric Kruskal-Wallis *H* test showed that the mean DADDS-C score differed by age and educational level but not by cancer type and sex (**Table 1**).

Psychometric Properties of DADDS-C

Exploratory Factor Analysis (EFA) for DADDS-C

EFA using SP resulted in three factors which accounted 72.437% of variance in DADDS. Factor 1, accounting 32.124% variance in DADDS-C, consisted of items 1–7 about the shortness of time; Factor 2, accounting 29.534% of the variance in DADDS-C, consisted of items 10–15 that were about distress about dying and death; Factor 3, accounting 10.778% variance in DADDS-C, consisted of items 8 and 9, which were about the sense of being a burden to others, which was different from two factors reported by Shapiro (29) and one factor reported by Engelmann (21). High factor loadings (**Table 2**), ranged from 0.615 to 0.865. The 3 items with the highest factor loadings in each factor were: item 12 (in factor 2)-Be prolonged or drawn out (0.865); item 8 (in factor 3)-Being a burden to others (0.855); item 2 (in factor 1)-Not having said all that I want to say to the people I care about (0.811), which were helpful for defining factors names. Cronbach's alpha for the three factors were: factor 1–0.925, factor 2–0.659, and factor 3–0.898. PA suggested one factors being extracted and MAP suggested two factors. As one factor-model accounted only 38.898% of variance and two factors-model accounted 65.684%. We rejected the one factor-model and compared two factors-model and three factors-model using CFA below.

Validity

Criterion validity was established as DADDS-C was positively correlated with [PHQ-9 ($r = 0.602$, $p < 0.001$), GAD-7 ($r = 0.676$, $p < 0.001$), subscale of QUAL-EC ($r = 0.172$, $p = 0.009$), subscale of QUAL-EC ($r = 0.542$, $p < 0.001$), and FACIT-sp ($r = -0.328$, $p < 0.001$), subscale of QUAL-EC($r = -0.304$, $p < 0.001$), subscale of QUAL-EC($r = -0.345$, $p < 0.001$)]. The three factors-model was analyzed by CFA firstly. Standard loading coefficients of items ranged from 0.597 to 0.890, indicating preferable correlation between items and factors (**Figure 1**). Acceptable convergent validity was confirmed by Average Variance Extraction (AVE) of 0.502–0.625 and Construct Reliability (CR) of 0.712– 0.906. AVE square root of three factors were: factor 1–0.790, factor 2–0.708, and factor 3–0.748. Correlation coefficients of factors ranged from 0.516 to 0.740. Minimum value of AVE square root (0.708) was smaller but very

TABLE 2 | Exploratory factor analysis of DADDS-C by Scree Plot (Eigenvalue > 1).

Item	% of Variance	Cumulative %	Loading of factor 1	Loading of factor 2	Loading of factor 3
1. Not having done all the things that I wanted to do	32.124%	32.124%	0.805	0.156	0.274
2. Not having said all that I want to say to the people I care about			0.811	0.248	0.176
3. Not having achieved my life goals and ambitions			0.799	0.301	0.114
4. Not knowing what happens near the end of life			0.697	0.395	0.148
5. Not having a future			0.645	0.521	0.123
6. The missed opportunities in my life			0.615	0.329	0.249
7. Running out of time			0.674	0.573	0.086
10. My own death and dying	29.534%	61.657%	0.473	0.649	0.150
11. Happen suddenly or unexpectedly			0.501	0.672	0.080
12. Be prolonged or drawn out			0.189	0.865	0.139
13. Happen when I am alone			0.338	0.747	0.005
14. Happen with a lot of pain or suffering			0.140	0.829	0.290
15. Happen very soon			0.553	0.700	0.042
8. Being a burden to others	10.778%	72.437%	0.090	0.157	0.855
9. The impact of my death on my loved ones			0.427	0.092	0.726

The Kaiser-Meyer-Olkin Measure of Sampling Adequacy was 0.919, and Bartlett's test was significant (Chi square = 1461.561, p = 0).

close to the maximum value of factors correlation coefficient (0.740), indicating acceptable discriminant validity of DADDS-C. χ^2/df (1.617), SRMR(0.049), RMSEA(0.069), CFI(0.966), TLI (0.954) indicated acceptable overall model fitting validity (**Figure 2**); two factors-model though had a better discriminant validity, had poorer value than three factors-model with χ^2/df (3.481), SRMR (0.081), RMSEA (0.140), CFI (0.769), TLI (0.816) (**Table 3**).

Reliability

Cronbach's alpha for the total scale was 0.938; Omega Hierarchical was 0.880, Omega Total was 0.959. These results showed DADDS-C had great internal consistency reliability.

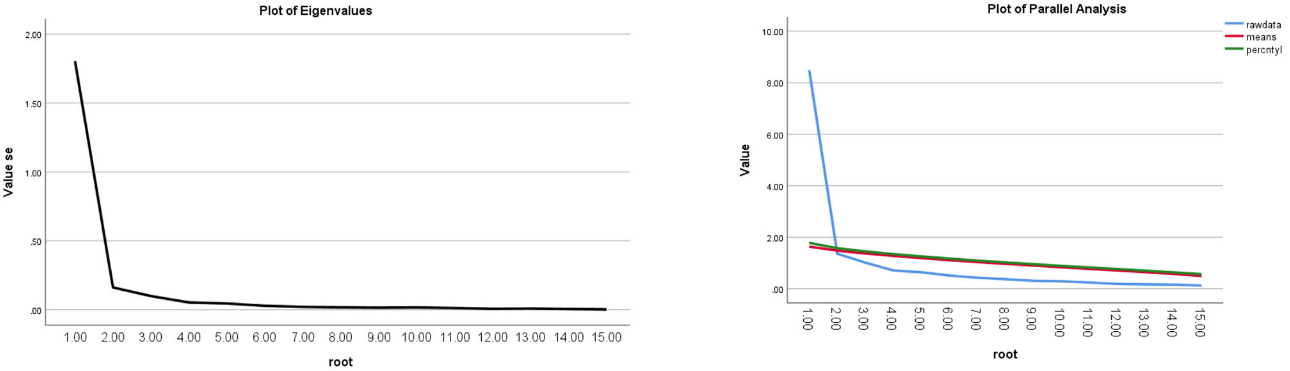
Risk Factors for Death Anxiety Among Advanced Cancer Patients

Of the total sample, 43 (16.8%) who scored $\geq$45 on the DADDS-C was defined positive cases; others were defined as negative cases. Age, education level, medical insurance coverage, PHQ-9 total score, suicide ideation, GAD-7 total score, four subscales for QUAL-EC (symptom burden, relationship with healthcare provider, preparation for end-of-life, life completion), FACIT-sp, which had a significant correlation with the DADDS-C score, were entered into univariate and multivariate Logistics regression analyses for risk factors exploration. Since DADDS-C scores significantly differed by age and educational level, they were also included in the logistics analyses. Multivariate Logistic regression results showed better relationship with health professionals (OR = 0.870, $p = 0.021$) preparation for end of life (OR = 1.225, $p = 0.008$) were associated with less death anxiety (**Table 4**).

DISCUSSION

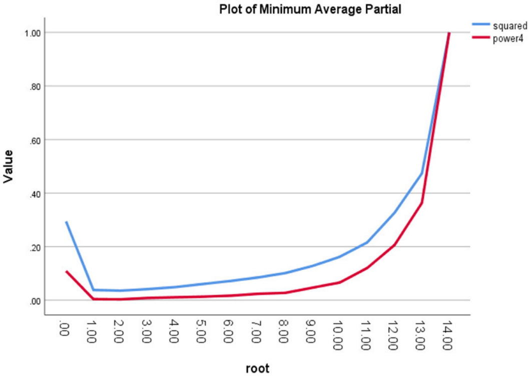
The present study demonstrated the validity of the DADDS-C assessing death anxiety in Chinese patients with advanced cancer. The analyses identified three factors on the DADDS-C, two of which correspond to the two factors of Finitude and Dying identified in a recent validation study of the DADDS (29). A third factor of worry about their loved ones was also identified in the present study. Though only two items in the third factor suggesting the potential instability in the subscale of DADDS-C, we have reasons to retain the three factors-model as follow: firstly, CFA result has confirmed this three factors-model was better than two factors-model in our sample; secondly, based on terror management theory, self-esteem containing experiencing sense of meaning and value was positive to protect individuals from death anxiety. Researchers verified that meaning of life, mediated by self-esteem, played positive role on death anxiety in Chinese elderly (40). This is consistent with the finding of Hu et al. that love and fulfilling the family mission were main sources of meaning in life for patients with advanced cancer; being a burden to the beloved ones and causing impact on others, which signified negative influence on family mission, meant loss of meaning of life in Chinese culture (41). Thirdly, the meaning of worrying about beloved ones (item 8 and item 9) was far different from finitude and dying distress. Except for absolutely following strict statistics methods, culture and clinical practice should also be considered to define factors structure. Therefore, we thought this factor should be preserved in DADDS-C for better understanding death anxiety in Chinese advanced cancer patients.

Almost 17% of the participants in this study reported at least moderate death anxiety and these individuals reported a worse relationship with their health care providers and being less prepared for the end of life. Psychological and spiritual concerns are subjective feelings that must be reported by patients themselves. These concerns can be captured in what have been termed patients-reported outcomes (PROs) (42), although distress about dying and death have not been routinely assessed. The present study has demonstrated the validity of the DADDS-C to capture this outcome in our sample. Few



The recommended number of factors is **3**

The recommended number of factors is **1**



The recommended number of factors is **2**

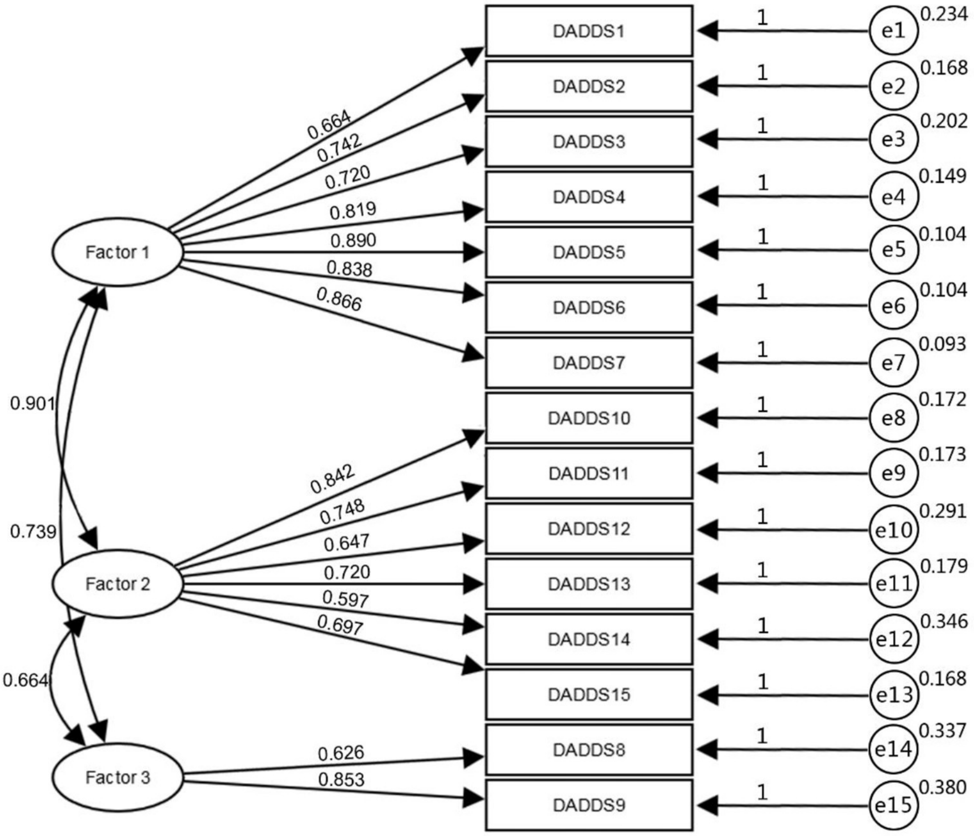
FIGURE 1 | Plots of three methods to define factors numbers.

well-designed researches on death anxiety was reported among Chinese advanced cancer patients. DADDS-C as a validated instrument would be useful and necessary to facilitate future researches. Discrepancy between our factor structure and western results indicated culture difference to a certain extent. So, using the same instrument world widely used would contribute to further understanding of different cultures' influence on all aspects of death anxiety. Death anxiety was correlated with depression and anxiety, as in other studies (19, 43), but this association was no longer present in logistic regression analyses. Better relationship with healthcare provider and preparation for end-of-life were independent protective factors for death anxiety, suggesting that clinical interventions supporting these factors may be of therapeutic value; researches and clinical management for depression and general anxiety could not fully cover the connotation of death anxiety.

Though conversation about death and dying is often avoided in China (44, 45), the high participant acceptability and 82.5% valid ratio for data collection demonstrated feasibility of utilizing the DADDS-C among Chinese advanced cancer patients. This outcome has been shown to be positively affected by the Managing Cancer and Living Meaningfully (CALM) intervention and will be an important outcome in the randomized controlled trial that we plan to conduct in China.

Strengths and Limitations

This study is the first validation and application report in China on a special death anxiety measurement designed for patients with advanced cancer and we used relatively rigorous statistical methods and strategy to verify the psychometric properties of DADDS-C. However, limitations deserved further exploration and were collected as follows: (1) Most of the participants were females with breast cancer, in middle age, living with a spouse, having high education, and living in cities. Though we found no association of death anxiety with sex and diagnosis, there should be caution regarding the generalizability of the results. (2) The participants were recruited from ambulatory clinics and inpatients ongoing anti-cancer treatments in our hospital and therefore may not be representative for advanced cancer patients with poor performance status. (3) Only 27 participants completed the DADDS-C a second time 15 days later so that re-test reliability could not be established. (4) Only two items in factor 3 showed potential instability in this subscale; more future studies is needed to focus on this so as to promote general utilization of DADDS-C. (5) This validation study was based on Classic Theory (CTT); Item Response Theory (IRT) was highly recommended by former researchers (46–48) and would be performed in the future research for discriminative value of DADDS-C. (6) Though



Unstandardized estimates Default Model

$\chi 2/df=1.617$; SRMR=0.049; RMSEA=0.069; CFI=0.966; TLI=0.954

FIGURE 2 | Three factors model in confirmatory factor analysis.

TABLE 3 | Comparing Model fits between three factor-model and two factors-model through confirmatory factor analysis.

Parameter	χ^2	df	χ^2/df	SRMR	RMSEA	CFI	TLI
Criteria	–	–	≤2.0	<0.08	≤0.06	≥0.95	≥0.95
Model fits of the three factors-model	126.157	78	1.617	0.049	0.069	0.966	0.954
Model fits of the two factors-model	309.770	89	3.481	0.081	0.140	0.844	0.816

DADDS-C was obviously a state-like scale as the purpose of developing this scale (capturing death anxiety phenomenon) reported by Lo (28), it was suggested to verify its nature by statistics methods (49). Further researches are needed on the DADDS-C on a more representative sample, with qualitative data regarding the acceptability of the DADDS-C, establishing its re-test reliability, and performing IRT and other statistics methods to get more information and implication about this instrument. There should also be exploration of how demographic and cultural factors may shape the nature and prevalence of death anxiety among Chinese people with advanced cancer.

Clinical Implications

Three factors-model DADDS-C is practical and preferable to be used for future studies among Chinese patients with advanced cancer. Standard measurement available under our culture background could facilitate more attention to death and dying researches and trigger more focus on this issue in clinical practice for high-quality cancer care. DADDS-C has been used as one of the main outcome measurement for in our RCT of CALM therapy in Chinese patients with advanced cancer. We found better relationship with health professionals and preparation for end of life were associated with less death anxiety, which provided useful information for the interventional study.

TABLE 4 | Results of risk factors for death anxiety from Univariate and Multivariate Logistics Regression Analysis.

Variables in the Equation		B	S.E.	Wald	df	Sig.	Exp(B) (Crude/ Adjusted OR)	95% C.I. for EXP(B)	
								Lower	Upper
Step 1[a]	Age	−1.406	0.292	23.251	1	$P < 0.0001$	0.245	0.138	0.434
		−0.706	0.379	3.467	1	0.063	0.494	0.235	1.038
	Education level	0.371	0.136	7.470	1	0.006	1.450	1.111	1.892
		0.358	0.187	3.672	1	0.055	1.431	0.992	2.064
	Medical insurance	0.553	0.339	2.672	1	0.102	1.739	0.896	3.377
		0.684	0.466	2.157	1	0.142	1.983	0.795	4.943
	PHQ9-total score	0.201	0.033	36.327	1	$P < 0.0001$	1.222	1.145	1.305
		0.072	0.063	1.280	1	0.258	1.074	0.949	1.217
	Suicide ideation	0.961	0.211	20.661	1	$P < 0.0001$	2.615	1.728	3.958
		0.084	0.368	0.052	1	0.819	1.088	0.529	2.236
	GAD7-total score	0.231	0.036	40.837	1	$P < 0.0001$	1.260	1.174	1.353
		0.088	0.063	1.923	1	0.166	1.092	0.964	1.236
	Symptom burden-QUAL	0.151	0.059	6.559	1	0.010	1.163	1.036	1.305
		0.036	0.086	0.179	1	0.672	1.037	0.876	1.227
	Relationship with HP-QUAL	−0.153	0.040	14.645	1	$P < 0.0001$	0.858	0.793	0.928
		−0.146	0.060	6.036	1	0.014	0.864	0.769	0.971
	Preparation-for-EOL-QUAL	0.334	0.061	30.507	1	$P < 0.0001$	1.397	1.241	1.573
		0.196	0.074	6.984	1	0.008	1.216	1.052	1.406
	Life-Completion-QUAL	−0.084	0.034	5.902	1	0.015	0.920	0.860	0.984
		0.051	0.061	0.705	1	0.401	1.053	0.934	1.186
	FACIT-sp total score	−0.090	0.022	17.466	1	$P < 0.0001$	0.914	0.876	0.953
		−0.004	0.034	0.013	1	0.908	0.996	0.933	1.064
	Constant	−5.127	2.388	4.611	1	0.032	0.006		

[a] *Variable(s) entered on step 1: age, education level, medical insurance, PHQ9-total score, Suicide ideation, GAD7-total score, Symptom burden-QUAL, Relationship with HP-QUAL, Preparation for EOL-QUAL, Life Completion-QUAL, FACIT-sp total score.*

CONCLUSION

DADDS-C is a practical measurement for death anxiety with good reliability and validity and it could be used in both researches and clinical practice. High prevalence of death anxiety among Chinese patients with advanced cancer reminds medical staff and caregivers associated with cancer care to give more attention to this issue.

DATA AVAILABILITY STATEMENT

Data supporting findings of this study and supplementary material are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Peking University Cancer Hospital Ethics Committee (No. 2018YJZ24). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LT: conceptualization, funding acquisition, investigation, project administration, resources, data curation, methodology, supervision, validation, writing, and review and editing. YZha: data curation, formal analysis, methodology, validation, writing, and reviewing and editing. YP: validation, data curation, methodology, and review and editing. YZho, JL, LS, YH, ZL, and YW: participants recruiting and review. All authors contributed to the article and approved the submitted version.

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Evaluation of Psychosocial Pathways to Family Adaptation of Chinese Patients With Liver Cancer Using the McCubbin's Family Resilience Model

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Background and Aim: With the prolonged survival time of patients with liver cancer, these families may face tremendous pressure and development dilemmas that can easily lead to family adaptation crises. Correspondingly, family adaptation crises adversely affect the quality of life of patients and family members. Basing on McCubbin's resilience model of family stress, adjustment, and adaptation, and considering the key factors affecting family resilience based on a review of literature, this study involved a construction of a family adaptation influencing factors model in Chinese liver cancer patients, which was then verified and revised.

Methods: This cross-sectional study was conducted between August and December 2020. Using convenience sampling, we selected 265 liver cancer families from the liver tumor center of a teaching hospital affiliated with a university in Shanghai, China. Data from 252 patients with liver cancer and their caregivers were used to identify the factors and pathways associated with family adaptation. The relationships were modeled using structural equations.

Results: A total of 265 liver cancer families participated in the survey, and 252 valid questionnaires were returned, with a response rate of 95.09%. The pathway regression coefficients of six factors (family burden, individual resilience, family problem-solving and coping, inner family support, outer family social support, and family function) in the model were found to be statistically significant ($P < 0.05$), indicating that all of them were significantly associated with family adaptation. Among them, inner family support, outer family social support, and family function were direct influencing factors, while the others were indirect. The path coefficients of the total effect of the determinants on family adaptation were as follows (from largest to smallest): individual resilience (0.562), family function (0.483), outer family social support (0.345), family burden (−0.300), inner family support (0.293), family problem-solving and coping (0.127).

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Conclusions: Our findings suggest that clinical nurses should not only pay particular attention to direct influencing factors, develop strategies to strengthen the overall family function, encourage patients and caregivers to utilize inner family and outer family social support, but should also consider indirect influence factors, focus on the vital role of the individual, and promote patients' and caregivers' personal and family coping ability.

Keywords: family resilience, family adaptation, liver cancer, model, influencing factors

INTRODUCTION

According to global cancer data in 2020, primary liver cancer (henceforth referred to as liver cancer) is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide, with approximately 906,000 new cases and 830,000 deaths in that year (1). Patients with liver cancer experience adverse symptoms and psychological burdens, low health-related quality of life, and high cost of treatment, which has become a major public health burden on a global scale (2, 3). China is one of the high-incidence areas, accounting for over 50% of new cases and deaths worldwide. Although liver cancer incidence and mortality rates have shown a decreasing trend, scholars estimated that the burden of liver cancer in China would still be severe by 2030 (4). With the growing sophistication of medical technology, the overall survival rate of liver cancer has increased, and survival time has been prolonged. As reported by Lencioni et al. (5), the survival rates of patients with liver cancer reached 70.3, 51.8, and 40.4% in the 1st, 2nd, and 3rd years after interventional therapy, respectively. In this situation, many families would be required to coexist with patients with liver cancer for a prolonged period.

Patients with liver cancer experience adverse physical symptoms and psychological problems in disease treatment and rehabilitation (6), and caregivers may experience anxiety and depression due to the influences of care burden, the uncertainty of the patient's disease progression, and development deprivation (7). At the same time, the diagnosis of liver cancer not only affects the individuals in the family, but also affects their relationship and family dynamics, which may lead to deterioration of the relationship between family members and changes in family lifestyles and values. Being a primary social group to maintain individual survival and development, the family is an important functional unit for achieving emotional communication and meeting the various development needs of family members. In the particular period, wherein cancer is confirmed, the family plays a powerful role and serves as the core force to help patients and family members deal with cancer. Families may face a severe crisis if they cannot effectively adapt to meeting the impact of liver cancer. Meanwhile, crises may further reduce their quality of life and life satisfaction (8). Therefore, the promotion of family adaptation to patients with liver cancer has become a problem lately.

Studies about liver cancer have mainly been conducted from a personal perspective, focusing on patients' symptoms, their negative psychological reactions, or caregiver burden (6, 7, 9). In recent years, some researchers have begun to explore the key role of family function in the treatment and recovery of cancer patients from the family's perspective as a whole (10). Upon analyzing the scientific literature, it appears that previous studies on families of patients with liver cancer mostly pay attention to the negative aspects of family experience and often ignore its internal advantages and positive factors. With the development of positive psychology, many researchers in medicine have shifted their focus from problems *per se* to the positive impacts produced by the family while coexisting with the patient, believing that the family has the potential to grow in adversity.

Family resilience is defined as individuals' and families' capacity to draw on mutual strengths to cope with or adapt to adversity using various resources in the interaction of multiple systems when encountering stressors. It is not a static structure but a process of positive interaction between individuals, families, and the external environment (11). An investigation on families of patients with stroke (12) revealed that family resilience is an essential factor that can positively and independently predict family adaptation. This conclusion has been verified in a study on families of patients with cancer (13), dementia (14), and children with illnesses (15, 16). Li et al. (17) studied the relationship among family resilience, individual resilience, and caregiver burden in breast cancer patients and found that family resilience and individual resilience can effectively alleviate the burden on caregivers and improve their quality of life. The study by Yan et al. (18) on families of patients with breast cancer also emphasized the importance of family resilience and concluded that intervention programs based on family resilience should be designed to enhance family adaptability and improve quality of life.

At present, a problem we must face is how to solve the plight of families with liver cancer patients and promote their family adaptation. The number of studies on family adaptation of liver cancer in China is few, and there is a lack of theoretical and systematic guidance. In this context, from the perspective of positive psychology, applying the theory of family resilience to the exploration of the family adaptation of patients with liver cancer may focus on exploring family advantages and support resources in disease treatment and rehabilitation. Additionally, it may explore new ways to enhance family adaptation, improve quality of life, and provide references and basses for research on families of patients with liver cancer.

Conceptual Framework

This study used McCubbin's resilience model of family adjustment and adaptation to determine the multiple factors that affect family adaptation in patients with liver cancer. This model is developed from the ABC-X model (19), including two phases: the adjustment phase and the adaptation phase. The adjustment stage means that the family can achieve a good state through fine-tuning when facing mild or short-term stress. The adaptation stage means that if major stressful events lead to maladjustment, the family will change the way it operates. In this manner, family resilience to cope with the pressure is stimulated to regain balance and harmony. Family resilience is affected by family function, resources, cognition, problem-solving ability, and coping. This study uses the "adaptation stage" as the basic theoretical framework. The family burden, which is caused by liver cancer, would influence family adaptation by stimulating and adjusting the process of family resilience.

Mccubbin and Mccubbin (20) defined family resilience as the process by which individuals, families, and the external environment interact positively. Wu et al. (21) and Benzies and Mychasiuk (22) also redefined the protective factors of family resilience from three levels: individual, family, and social, affirming the important role of individuals as the basic functional unit of families. The stimulation and adjustment of family resilience is a process from the individual to family levels; however, there is no specific description of personal factors in McCubbin's model. Therefore, this study adds personal factors to the basic model. Resilience reflects positive beliefs of an individual or family when faced with adversity or crisis. It refers to an individual's ability to maintain and restore mental and physical health when faced with stress or adversity (23). It is an internal resource related to personality and can change the mindset of patients and their families in response to stressful events. Studies conducted by Yao and Qiu (24) and Chen et al. (25) suggest that enhancing personal resilience is an essential influencing factor in enhancing family resilience. Therefore, this study hypothesized that individual resilience is an important intermediary factor between family burden and family outcomes. Family burden affects the behavior of family members by affecting individual resilience and has an effect on family adaptation by influencing other factors.

At present, studies have confirmed the positive predictive effect of personal resilience on other family factors. Studies show that higher levels of individual resilience indicate better family function, higher levels of perceived support, and better family problem-solving and coping abilities (26–28). According to McCubbin's family resilience theory, other family factors work together to cope with the adverse effects of stressful events through interaction to promote the family to achieve an excellent adaptive state (11). Among them, family problem-solving and coping can affect support and resources as perceived by the family. Over time, it causes changes in family functions and the relationship between the family and the outside world (29). Zhang et al. (30) pointed out that social support is a key factor affecting family functioning. Meanwhile, the outer family social support system also affects the perception of inner family support system, which in turn affects family function and family adaptation (31).

Therefore, based on "McCubbin's resilience model of family adjustment and adaptation" and the literature review, this study proposed a model of influencing factors of family adaptation for patients with liver cancer (**Figure 1**). This study made assumptions about the relationship between variables based on the theoretical model: ① Family burden, caused by liver cancer, would affect individual resilience, which would, in turn, affect other family factors and ultimately affect family adaptation. ② Individual resilience of patients with liver cancer and caregivers would affect family adaptation by affecting family problem-solving and coping, outer family social support, inner family support, and family function. ③ Family problem-solving and coping, outer family social support, inner family support, and family function of liver cancer families interact and ultimately, directly and indirectly, affect the family adaptation of liver cancer families. ④ Family problem-solving and coping would affect outer family social support, inner family support, and family function. Outer family social support would affect inner family support and family function, and inner family support would affect family function.

Therefore, this study intends to comprehensively review the literature, construct and verify an influencing factor model of family adaptation of patients with liver cancer based on the family resilience theory, so as to provide new ideas and perspectives for improving the family adaptation of liver cancer families.

MATERIALS AND METHODS

Participants and Procedure

The targeted population was the families of patients with primary liver cancer, including patients and their caregivers. Family members were recruited from the liver tumor center of a teaching hospital affiliated with a university in Shanghai, China. They were eligible to participate in this study if they fulfilled the following criteria: (a) a family member ($\geq$18 years old) was diagnosed with primary liver cancer, (b) had a fixed primary family caregiver ($\geq$18 years old), (c) was able to communicate in the language required for the study, and (d) volunteered to participate in this study. The exclusion criteria were as follows: (a) the caregiver was paid, and (b) the patient or caregiver had a history of psychiatric problems.

This study used the structural equation model for statistical analysis, and the sample size was calculated based on it. There is no precise formula for estimating the sample size required for the structural equation model analysis. Wu (32) reported that the sample size needed for structural equation model analysis is preferably $>$200. Therefore, the sample size of this study was estimated to be more than 200 cases.

After the approval of the ethics committee, the investigator collected the data using self-assessment questionnaires in the liver cancer wards. The questionnaires for patients included the general situation questionnaire and the Resilience Scale Specific to Cancer. The questionnaires for caregivers included a general situation questionnaire, Family Burden Scale of Disease, 10-item Conner-Davidson Resilience Scale, Family Crisis-Oriented Personal Evaluation Scales, Perceived Social Support Scale, Family APGAR (adaptation, partnership, growth, affection, resolve) Index, and Family Adaptation Scale. Fifteen families were pre-surveyed before the formal investigation. During the investigation, researchers selected eligible participants in accordance with the inclusion and exclusion criteria, and

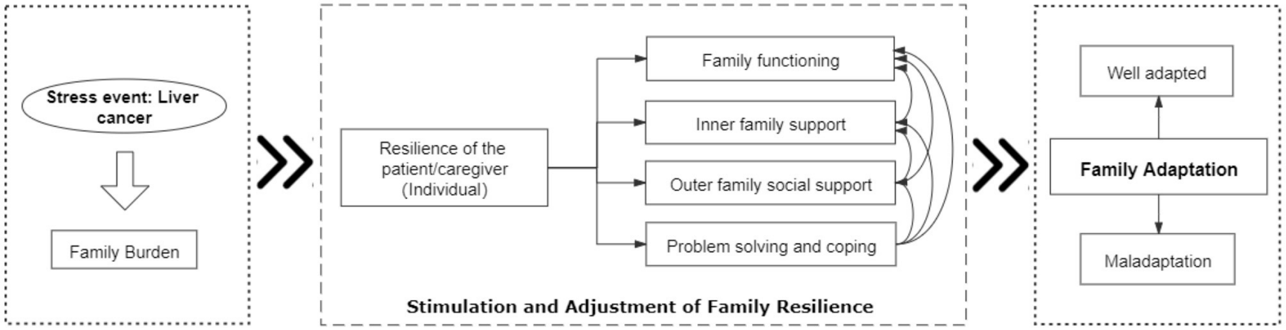

FIGURE 1 | Model of influencing factors of family adaptation based on the Family Resilience Model—Conceptual framework.

conducted on-site investigations using a unified protocol. Those who had difficulty writing due to educational level, eyesight, or other reasons were assisted by researchers to complete the questionnaire. A total of 265 pairs of liver cancer patients and their families participated in the survey, and 252 pairs of valid questionnaires were returned, with a response rate of 95.09%. Invalid questionnaires were defined as having missing data of more than 10% for one or more variables.

Measures

Resilience Scale Specific to Cancer

A 10-item Resilience Scale Specific to Cancer, RS-SC-10 (33), was used in this study. RS-SC-10 contains 10 items with high discriminative parameters from the RS-SC and consists of two factors: Generic and Shift-Persist. The participants responded to the questionnaire using a 5-point Likert scale (from 1 = never to 5 = always), with the possible score range being 10–50. Higher scores indicate a higher level of resilience. The Cronbach's alpha coefficients were 0.85 (Generic) and 0.89 (Shift-Persist), respectively, based on the current participants.

10-Item Conner-Davidson Resilience Scale

The 10-item Conner-Davidson Resilience Scale, CDRISE-10 (34, 35), consists of ten items rated on a 5-point Likert scale (from 1 = not at all true to 5 = strongly agree). It was developed as a brief version of the full 25-item CDRISE. The Chinese version was used in this study to measure caregivers' levels of resilience. The concurrent validity and internal consistency reliability of the Chinese version of the CDRISE-10 have been shown to be adequate (35). Based on this study, the internal consistency coefficient was 0.81.

Family Burden Scale of Disease

The Family Burden Scale of Disease, FBS (36), was used to assess family burden and stressors in six areas: family economic burden (six items), family daily activities (five items), family leisure and entertainment activities (four items), family relationships (five items), family members' physical health (two items), and family members' mental health (three items). The participants responded to the questionnaire using a 3-point Likert scale (from 0 = no burden to 2 = severe burden), and the score ranged from 0 to 50. A high score indicates a higher level of burden. Based on the current participants, the internal consistency coefficient of each dimension ranged from 0.69 to 0.7 (37).

Family Crisis-Oriented Personal Evaluation Scales

The Family Crisis-Oriented Personal Evaluation Scales, F-COPES (11), is a self-assessment scale used to measure the levels of family problem-solving and coping, and is completed by family members. Wang et al. (38) revised the scale into a Chinese version, which includes five dimensions: getting support (including support from family, relatives, friends, and neighbors), positive cognition, seeking support from spirit and belief, seeking social support (including support from other families, social institutions, doctors, and professionals), negative cognition, and avoidance. On this scale, participants were asked to report whether they agreed (from 1 = not at all true to 5 = strongly agree) to applying the family problem-solving and coping behaviors described for each item. The score range is 27–135. A higher score indicates a higher level of family problem-solving and coping. Based on the results of the current study, the internal consistency coefficient was 0.842.

Perceived Social Support Scale

The Perceived Social Support Scale, PSSS (39, 40), is a tool to measure self-perceived multi-level social support. There are 12 items in the scale, which can be divided into two dimensions: inner family support and outer family social support. The total score reflects the overall level of social support that individuals feel. The participants responded to the questionnaire using a 7-point Likert scale (from 1 = not at all true to 7 = strongly agree), with the possible score range being 12–84. A high score indicates a higher level of self-perceived social support. This scale is widely used worldwide, and has proven to be reliable and valid. Based on this study, the internal consistency coefficient was 0.88.

Family APGAR Index (APGAR)

The Family APGAR Index, APGAR (36), evaluates family function in five areas given as follows: adaptability, partnership, growth, emotion, and cohesion. The participants responded to the instrument using a 3-point Likert scale (0 = almost rarely, 1 = sometimes, 2 = usually). The scores are added together, with 0–3 points indicating severe family dysfunction, 4–6 points indicating moderate family dysfunction, and 7–10 points indicating good family function. Based on this study, the internal consistency coefficient was 0.813.

Family Adaptation Scale

The Family Adaptation Scale FAS (41), is used to assess the level of family adaptation of the disabled family, which is completed by family members. The scale was revised by Wang et al. (42) in Chinese and has been found to have satisfactory internal consistency reliability. The revised version consists of 15 items that describe satisfaction with family life using a 7-point Likert scale (from 1 = not at all to 7 = totally satisfied). The total score is the sum of all items. A higher score indicates a higher level of family adaptation. Based on this study, the internal consistency coefficient was 0.951.

Data Analyses

A structural equation model was applied to confirm the hypothesis model using Amos version 24.0. Harman's single factor test method was used to test common method bias. Descriptive statistics were computed for the variables and reported as means, standard deviations, kurtosis, and skewness. Then, to build the best-fitted structural model, we proceeded step-by-step. First, a measurement model of family resilience was developed to assess family resilience. Second, the hypothesized model of family adaptation based on the family resilience model was developed. Then, the measured values were substituted into the model to perform structural equation model analysis to estimate the degree of fit between the hypothetical model and the actual data. The model was revised until the degree of fit met the standards. After validating the final model, the total effects of the factors (direct plus indirect *via* mediating relationships) were calculated from the standardized regression coefficients. The difference was statistically significant ($P < 0.05$).

To evaluate the model fit, a set of fit indices were used based on recommended criteria (32), including the following: the Chi-Square to df Ratio (χ^2/df), when values between 1 and 2 indicate that the model fits well; a comparative fit index (CFI) ≥0.90; goodness-of-fit index (GFI) ≥0.90; adjusted goodness-of-fit index (AGFI) ≥0.90; the Tucker–Lewis index (TLI) ≥0.90, which showed an acceptable fit of the model; the root mean square error of approximation (RMSEA), where values between 0.05 and 0.08 indicate that the model is acceptable, with <0.05 regarded as an appropriate fit; and the standardized root mean square residual (SRMR) of <0.05.

According to the literature review, the indirect effect value = (action path coefficient of the independent variables, which act on the first mediator variable on the indirect pathway) × (total effect on the family adaptation of the first mediator variable that was affected upon by the independent variable). The total indirect effect value is the sum of the indirect effect values of all paths from the independent variable to the dependent variable. For example, outer family social support (OFSS) acts on family adaptation (FA) indirectly through inner family support (IFS), and its indirect effect on FA should be the direct effect of OFSS to IFS multiplied by the total effect of IFS to FA. That is, the indirect effect value = 0.488*0.293 = 0.143.

TABLE 1 | Demographic and cancer-related characteristics.

Variable	**Liver cancer patients (*n* = 252)**	**Family caregivers (*n* = 252)**
	***N* (%)**	***N* (%)**
Age (years)		
≤40	24 (9.5)	106 (42.0)
41–64	172 (68.3)	134 (53.2)
≥65	56 (22.2)	12 (4.8)
Gender		
Male	222 (88.1)	78 (31.0)
Female	30 (11.9)	174 (69.0)
Educational level		
Junior high school or below	136 (54.0)	89 (35.2)
High school	66 (26.2)	78 (31.0)
University degree or above	50 (19.8)	85 (33.8)
Time since diagnosis (months)		
≤6	98 (38.9)	
7–12	27 (10.7)	
13–24	45 (17.9)	
≥25	82 (32.5)	
Family type		
Nuclear	109 (43.3)	
Stem	115 (45.6)	
Extended	28 (11.1)	
Family income per month (CNY)		
≤1,000	37 (14.7)	
1,000–2,999	64 (25.4)	
3,000–4,999	73 (29.0)	
≥5,000	78 (30.9)	
Occupational status		
Retired at home or Left work due to caregiving duties		114 (45.2)
Part-time/full-time job		138 (54.8)
Relationship with patients		
Spouses		177 (70.2)
Grown-up children		62 (24.6)
Others (parents/sisters/brothers)		13 (5.2)

RESULTS

Demographic Characteristics

Mean ages of the family caregivers and cancer patients were 43.96 ± 11.87 and 56.33 ± 10.87 years, respectively. Other demographic and clinical information for caregivers and patients is shown in **Table 1**.

Common Method Bias Test Results

Results of the Harman's single factor test showed that the first common factor obtained without rotation explained 27.47% of the variance, which is less than the critical value of 40%. Therefore, we believe that there was no serious common method bias problem in this study.

TABLE 2 | Means, standard deviations, skewness, and kurtosis for observed variables.

Variables	M	SD	Skewness	Kurtosis
PR	35.96	7.226	−0.362	−0.359
CR	24.65	7.215	0.114	−0.428
OFSS	39.56	9.538	−0.447	0.117
IFS	22.06	4.732	−0.859	0.760
PSC	90.92	12.538	0.156	−0.152
FA	76.00	18.350	−0.890	0.695
Adaptability	1.52	0.561	−0.625	−0.652
Partnership	1.44	0.612	−0.610	−0.556
Growth	1.43	0.618	−0.595	−0.571
Emotion	1.51	0.582	−0.704	−0.480
Cohesion	1.60	0.587	−1.166	0.361
Economic burden	7.85	3.395	−0.476	−0.791
Daily Activity burden	3.86	2.492	0.253	−0.637
Leisure burden	3.56	2.288	0.081	−0.897

PR, patient resilience; CR, caregiver resilience; OFSS, outer family social support; IFS, inner family support; PSC, problem-solving and coping; FA, family adaptation.

Descriptive Analysis

Descriptive statistics for observed variables were tested to check for normality of distribution. For each of the observed variables, the kurtosis and skewness values were between 1 and −1.2; therefore, this sample can be defined as having a normal distribution. The collinearity test in this study showed that the tolerance was >0.1, and the variance expansion factor (VIF) value was <10, indicating no serious collinearity problem. Descriptive statistics for the observed variables are presented in **Table 2**.

Measurement Model

Confirmatory factor analysis was used to verify whether "family resilience" included the core sub-concepts described above. The model was assessed using the maximum-likelihood method. Since this model was used to verify whether the concept of "family resilience" includes the corresponding sub-core concepts, the correlation between these sub-core concepts was not considered.

A test of the measurement model showed an acceptable fit to the data (χ^2/df = 2.331, CFI = 0.963, GFI = 0.944, AGFI = 0.906, RMSEA = 0.073, SRMR = 0.0500), which supports the convergent validity of the indicators (**Figure 2**).

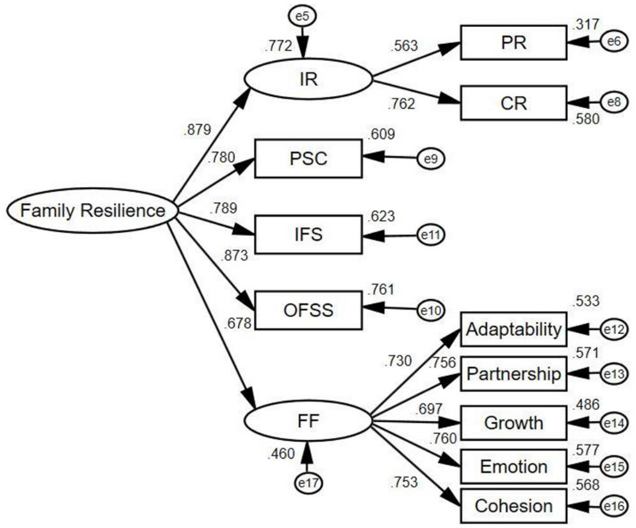

FIGURE 2 | Measurement model used to calculate the latent variable—family resilience. IR, individual resilience; PR, patient resilience; CR, caregiver resilience; OFSS, outer family social support; IFS, inner family support; PSC, problem-solving and coping; FF, family function.

Structural Model

This structural equation model analysis was applied to examine the effects of different factors on family adaptation and influential pathways. In the structural equation analysis, the hypothetical model was first tested, and included the possible paths among family burden, individual resilience, family problem-solving and coping, family function, inner family support, outer family social support, and family adaptation. Among them, four paths, including family problem-solving and coping to inner family support, family function, and family adaptation, as well as outer family social support to family function, are not significant. Based on previous literature and on our own findings, we deleted these paths. The final model is shown in **Figure 3**. The fit indices of the modified model were as follows: chi-square = 1.649, RMSEA = 0.051 [P(RMSEA) < 5%] = 0.573, SRMR = 0.043, CFI = 0.974, GFI = 0.939, and TLI = 0.966. Therefore, all paths were close to the ideal values, indicating that the modified model sufficiently fits the data.

Standardized direct effects, indirect effects, and total effects of standardization of all factors explaining the level of family adaptation are presented in **Table 3**, along with the path of effect generation. The results showed that the pathway regression coefficients of six factors (family burden, individual resilience, family problem-solving and coping, inner family support, outer

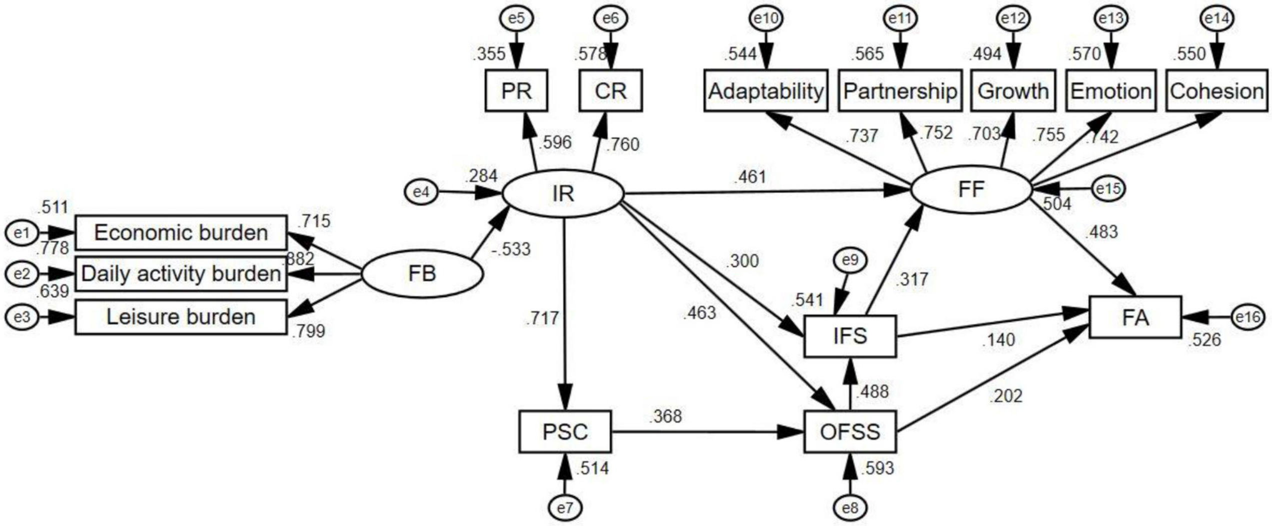

FIGURE 3 | Model of influencing factors of family adaptation based on the Family Resilience Model—Final version. FB, family burden; IR, individual resilience; PR, patient resilience; CR, caregiver resilience; OFSS, outer family social support; IFS, inner family support; PSC, problem-solving and coping; FF, family function; FA, family adaptation.

family social support, and family function) in the model were statistically significant ($P < 0.05$), indicating that all of them were significantly associated with family adaptation. Among them, inner family support, outer family social support, and family function were direct influencing factors, while the others were indirect influence factors. The path coefficients of the total effect of the determinants on family adaptation, from largest to smallest, were as follows: individual resilience (0.562), family function (0.483), outer family social support (0.345), family burden (−0.300), inner family support (0.293), problem-solving, and coping (0.127).

DISCUSSION

This study found that the average score of family adaptation was 76.00 (SD 18.35), and the average item score was 5.07, which was higher than the theoretical median (60 and 4). This score is consistent with the study by Wang involving patients with Alzheimer's disease (31). There is currently no cut-off value for this scale. Therefore, we cannot completely determine the level of family adaptation in patients with liver cancer. However, according to the rating method of the scale (from 1 = not at all to 7 = totally satisfied), four points mean that they have a neutral attitude toward the overall assessment of the family. It can be considered that the family members of the patients with liver cancer in this study were slightly satisfied with the overall adaptation of the family. The characteristics and structure of families of patients with liver cancer are vulnerable to the impact of cancer, which may lead to an adaptation crisis if effective measures are not taken in a sufficient period of time (43). According to the family system theory, the individual and system are intertwined and inseparable. The individual's quality of life is inevitably affected by the family's adaptation, and maladjustment of the family often affects the family members' quality of life (44). Therefore, exploring the influencing factors, paths, and effects of family adaptation is of practical significance and can provide a theoretical reference for family intervention programs for patients with liver cancer.

We developed a hypothetical model based on the McCubbin family resilience model to explain the factors that affect the family adaptation of patients with liver cancer, as well as tested the effectiveness of the model. In this model, family burden, individual resilience, and "problem-solving and coping" are indirect factors affecting family adaptation, while family function and support system directly affect family adaptation.

Family burden indirectly affects family adaptation through individual resilience, and the impact is relatively high. The studies by Ju et al. (45) and Tong (46) both showed that family burden is a significant risk factor for family resilience, but they did not explore the mediating role of individual resilience. However, the study by Hsiao and Van Riper (47) on families of children with Down syndrome found that when faced with a major stressful event, an individual's positive perception and significance of the family can help the family achieve a good state of adaptation. This finding is consistent with the accepted definition of individual resilience. A cancer diagnosis is a very stressful event for families with liver cancer, especially in China, where middle-aged men have a high incidence of liver cancer. These men are also the main source of income and spiritual support of the family. The diagnosis will then cause a serious burden on the family's economic status, daily activities, and entertainment (48). When facing serious negative stressful events, individuals will be affected first, which results in psychological and behavioral changes. Both Zhang et al. (49) and Wang et al. (50) studied the individual resilience of patients with cancer and found that family burden is an important

TABLE 3 | Effects of factors and pathways associated with family adaptation.

Factor	Standardized direct effects		Standardized indirect effects			Standardized total effects
	Pathways	Direct effect value	Pathways	Indirect effect value	Total indirect effect value	
FB	–	–	FB—The pathway from IR to FA—FA	−0.300 = −0.533*0.562	−0.300	−0.300
IR	–	–	IR—FF—FA	0.223 = 0.461*0.483	0.562	0.562
			IR—The pathway from IFS to FA—FA	0.088 = 0.300*0.293		
			IR—The pathway from OFSS to FA—FA	0.160 = 0.463*0.345		
			IR—The pathway from PSC to FA—FA	0.091 = 0.127*0.717		
PSC	–	–	PSC—The pathway from OFSS to FA—FA	0.127 = 0.345*0.368	0.127	0.127
OFSS	OFSS—FA	0.202	OFSS—The pathway from IFS to FA—FA	0.143 = 0.488*0.293	0.143	0.345
IFS	IFS—FA	0.140	IFS—The pathway from FF to FA—FA	0.153 = 0.483*0.317	0.153	0.293
FF	FF—FA	0.483	–	–	–	0.483

**This result means that an increase of one standard deviation of the outer family social support score led to an increase of 0.345 unit of family adaptation score.*

**FB, family burden; IR, individual resilience; OFSS, outer family social support; IFS, inner family support; PSC, problem-solving and coping; FF, family function; FA, family adaptation.*

factor affecting individual resilience, and a greater family burden correlated with lower individual resilience. Other studies have also confirmed a significant correlation between individual and family resilience. A study by Card and Barnett (51) showed that individual resilience plays an important role in family resilience, as it can help patients and family members actively evaluate and recognize stress, promote and develop family resilience, and family adaptability. Therefore, family burden can have an indirect effect on family adaptation by affecting individual resilience.

In this model, individual resilience had the highest impact on family adaptation. Although it has no direct effect on family adaptation, it plays a fundamental role in multiple influencing paths. Individual resilience can affect the perception of support systems, family problem-solving and coping, as well as family function by influencing individual psychological behavior, thus indirectly affecting family adaptation, which is similar to the findings of Kukihara et al. (52) and Han et al. (53). Resilience refers to an individual's ability to maintain and restore mental health in the face of stress or adversity (23). When facing major diseases, good individual resilience is an important family resilience factor. Higher levels of individual resilience indicate better family function, higher levels of perceived support, and better family problem-solving and coping abilities (26–28). However, it is generally believed that individual resilience is an intermediary factor between family resilience and other family outcomes, thus emphasizing the influence of family on individuals (54). However, as individual resilience is an essential factor affecting family resilience, people can explore more effective interventions to improve family resilience from this perspective (55, 56). The family system theory states that the individual and the family are intertwined. Being the functional unit of the family, the individual also plays a very important role in the process of family adjustment and adaptation (57). Meanwhile, when defining the concept of family adaptation, McCubbin considered it to be manifested as two levels of adaptation, that is, the "fitness" between individuals and the family as a whole, and between the family and its community or environment (20). To a certain extent, it also illustrates the importance of personal factors in promoting family adaptation. This also reminds clinical medical staff that in the field of family nursing practice for the care of cancer patients, researchers should not only regard the family as a whole, but also pay attention to the development and growth of individuals in the family, as well as clarify the role boundaries between the individual and family. This allows for the realization of two-way growth and well-rounded development of the individual and family, promoting family adaptation more effectively.

This study found that family problem-solving and coping indirectly affected family adaptation through outer family social support, with the lowest impact, which is consistent with the results of Mirsoleymani's study (58). This may be because higher levels of family problem-solving and coping abilities lead to greater ease for families of patients with liver cancer to perceive outside support, and thus, can actively use support resources to cope with pressure, thereby promoting family adaptation. In this study, the direct effects of "family problem-solving and coping" on inner family support, family function, and family adaptation were not significant, consistent with some previous studies' results (16, 38). Using the same scale with the families of older adults with dementia, Wang et al. (38) also reported a loss of direct effect of "family problem-solving and coping" on family resources and family adaptation, retaining only a direct effect on the outer family support system. This may be related to the limitations of the measurement scale itself. The scale used in this study is a revised Chinese version from an original foreign scale, which includes obtaining support, positive cognition, seeking support from spirit and belief, seeking social support (including support from other families, social institutions, doctors, and professionals), negative cognition, and avoidance. Most of them point to the cognition of family situation and search for support, which are highly correlated with outer family social support system. Meanwhile, traditional families often rely on their inner strength to solve and address various issues in Chinese cultural situations. Therefore, this scale may not be a good measure of Chinese family problem-solving and coping ability, which may lead to the final model retaining only one significant relationship between family problem-solving and coping with outer family social support. Following studies on family coping need to explore more localized and targeted measurement tools to further explore the family's problem-solving and coping skills when facing a crisis in family development and adaptation.

In this study, perceived support of liver cancer families was measured and divided into inner family support and outer family social support, both of which had direct and indirect effects on family adaptation. The role of support systems in family adjustment has been confirmed in many studies (31, 59, 60). The lack of inner family support networks and outer family social support can lead to family maladjustment. In particular, the less family support and social support people perceive, the easier it is for the family to have a low adaptation level, consistent with our research results. In this study, the direct effect of outer family social support on family function disappeared, and it affected family function and family adaptation through inner family support. This may be related to Chinese family culture. Many Chinese people believe that they have to solve their own family affairs. The inner family support system is the base of the outer family social support system, which in turn acts on the whole family through the former (61). Support from friends, communities, and society can provide families with informational and emotional assistance so that they can feel supported, thereby promoting communication and mutual support between family members and enhancing their perceived inner family support. A study by Mo'tamedi et al. (62) found that the inner family support system is an important factor in family resilience, and was positively correlated with family adaptation. This study also found that the overall effect of outer family social support on family adaptation was higher than that of inner family support. This may be because the impact of inner family support on family adaptation has a "ceiling effect." In this study, the score of perceived inner family support was 22.06, with a full score of 28, and the score of perceived outer family social support was 39.56, with a full score of 56. The level of perceived inner family support is higher than that of outer family social support, which is consistent with the findings of Fontes et al. (63). Therefore, the changes in outer family social support may cause greater effects on family adaptation than inner family support.

Family function can directly affect family adaptation, with this effect being relatively high, consistent with the results of Mirsoleymani's study (58). The definitions of family function and family adaptation are not clear in the literature. Some studies use family functions to reflect family adaptation, which may lead to misunderstandings. In this study, the concepts of family function and family adaptation are different, with a distinction needed to be made. As an outcome indicator, family adaptation refers to the harmony and balance of the family; that is, the state of balance and stability achieved by the family through coping and efforts when facing a crisis (20). On the other hand, family function is used to describe the family's current internal characteristics and structure, which refers to the emotional connection between family members, family rules, family communication and the effectiveness of dealing with external events (64). First, good family function can provide a supportive environment for patients and their families, which can not only ensure that patients receive more physiological care and emotional support, but can also help regulate the psychological stress responses of family members. It can also help patients and family members establish good role adaptations so as to promote effective interaction among family members, which then helps the family achieve a good state of harmony and balance (52, 65). Therefore, researchers should focus on the important role of family function in liver cancer families in clinical nursing practice, explore more plans to strengthen family function, help families deal with various stressful events effectively, and finally achieve a balanced and stable state.

CONCLUSIONS

Understanding the family adaptation to stressful events is central to promoting well-being in liver cancer families. In this study, family adaptation of liver cancer families was maintained at the level of mild satisfaction. It was affected by individual resilience, family function, support system, family problem-solving and coping ability. Therefore, in the practice of home care for liver cancer, clinical workers should pay not only special attention to direct influencing factors, adopt strategies to strengthen the overall family function, and encourage the active use of support systems, but also consider indirect influencing factors to improve patients' personal and family coping ability, reduce the burden on the family, and help the family maintain a harmonious and balanced state. Further research should explore the intervention strategies for the family adaptation of liver cancer patients, apply theories to practice, and continuously improve the care and services for liver cancer families.

LIMITATIONS AND FUTURE PERSPECTIVES

Upon critically analyzing the present study, several limitations must be considered when interpreting our findings. First, self-report tools were used, which are not exempt from limitations such as inaccurate reporting. Second, participation in this study was voluntary, and some maladaptive families refused to participate and were not included in this study according to voluntary principles. Consequently, the study's sample composition may not represent the characteristics of all the liver cancer families in China. Third, the family-related variables in this study were reported by family caregivers and may not describe the family's overall situation comprehensively and accurately. Follow-up studies should further explore the difference between the outcomes reported by patients and those reported by family caregivers.

With the advancement of medical standards, the survival time of patients with liver cancer has been prolonged, and an increasing number of families have to coexist with such patients for a long time. Promoting better adaptation for families of patients with liver cancer has become an important issue. More research on family resilience is being carried out in China, and an increasing number of researchers are beginning to pay attention to family resilience and family adaptation of the diseased population (17, 18, 38, 42). In the future, we should continue to explore how to develop intervention programs that effectively promote family adaptation for patients with liver cancer based on the family resilience theory.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Zhongshan Hospital Affiliated to Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SM developed the study design, organized the sample recruitment, collected data, and contributed to the writing of the manuscript's introduction, discussion, and references sections. HL contributed to the study design and writing of the manuscript's introduction, discussion, and reference sections. YZ, JY, and XL assisted in the data collection and research design. JP contributed to the writing of the manuscript's introduction, discussion, and reference sections. YL contributed to the research design and literature review of this study. All authors contributed to the article and approved the submitted version.

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