JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2022, 52(3)227–236
https://doi.org/10.1093/jjco/hyab198
Advance Access Publication Date: 28 January 2022
Original Article

OXFORD

Original Article

A randomized clinical trial of guided self-help intervention based on mindfulness for patients with hepatocellular carcinoma: effects and mechanisms

Zengxia Liu[1,2], Min Li[3], Yong Jia[1], Shuo Wang[1], Lufang Zheng[1], Cong Wang[1] and Li Chen[1,*]

[1]School of Nursing, Jilin University, Changchun, [2]School of Nursing, Changchun University of Chinese Medicine, Changchun and [3]Invasive Technology Department, The First Hospital of Jilin University, Changchun, China

*For reprints and all correspondence: Li Chen, Dean of School of Nursing, NO.965 Xinjiang Street, Changchun, Jilin 130021, China. E-mail: chen_care@126.com

Received 12 August 2021; Editorial Decision 24 November 2021; Accepted 26 November 2021

Abstract

Background: Compared with face-to-face mindfulness-based interventions (MBIs), online mindfulness interventions may be more convenient for patients with limited resources and can provide self-help mindfulness methods to improve the quality of life of cancer patients. This study investigated the effects of guided self-help mindfulness-based interventions (GSH-MBIs) on psychological distress, quality of life and sleep quality in patients with hepatocellular carcinoma and explored the underlying mechanisms.

Methods: A total of 122 patients with hepatocellular carcinoma were randomly divided into the intervention group or the conventional treatment group. Psychological distress, quality of life, sleep quality, psychological flexibility and perceived stress were evaluated in the groups before the intervention at baseline, after the intervention, at 1-month follow-up and 3-month follow-up. The intervention's effects over time and the potential mediating effects were analysed using generalized estimating equations (GEE).

Results: GEE results indicated significant time–group interaction effects on psychological distress ($P < 0.001$) and sleep quality ($P < 0.001$). The intervention significantly improved psychological flexibility (β, −2.066; 95% CI, −3.631, −0.500) and reduced perceived stress (β, −2.639; 95% CI, −4.110, −1.169). Psychological flexibility and perceived stress played a mediating role in the observed results.

Conclusion: GSH-MBIs can improve psychological distress and sleep quality via changing the psychological flexibility and perceived stress in hepatocellular carcinoma patients.

Key words: hepatocellular carcinoma, mindfulness-based intervention, self-help, psychological distress, sleep quality, quality of life

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third leading cause of cancer-related death, after lung cancer and colorectal cancer. HCC is characterized by severe symptoms, rapid progression and poor prognosis (1). Approximately 900 000 new cases of HCC and ~830 000 deaths related to HCC were reported in 2020 worldwide (2). China is one of the countries with the heaviest burden of HCC, as the number of HCC patients in China accounts for more than half of the global HCC patients (2). The level of distress is considerably increased in one-third of HCC patients even in comparison to those with other kinds of cancer (3). Anxiety and depression are two psychological distress that are frequently reported by HCC patients (4,5). The combination of psychological and physical issues reduce the quality of life of HCC patients. Therefore, it is very important to reduce cancer-related symptoms and improve mental health through effective psychological interventions, but there is no clear knowledge about the effect of psycho-oncological interventions in HCC patients (3). One study included only a small number of HCC patients in the follow-up assessment (6) The other study only reported clinically significant trends in the intervention group (IG) of the study (7). Therefore, the psycho-intervention effect on mental health of HCC patients is not clearly clinically objectifiable.

Mindfulness is defined as the ability to observe thoughts, bodily feelings or present feelings with an open and accepting attitude. Mindfulness-based interventions (MBIs) teach participants to recognize habitual response patterns and focus more on their daily lives (8,9). Several researchers have demonstrated the effectiveness of MBIs in reducing psychological distress and improving the quality of life of cancer patients (10,11). Most reviews demonstrated that mindfulness interventions can effectively reduce the psychological distress of cancer patients, including anxiety and depression symptoms (12–14).

Although MBIs have potential benefits for relieving psychological distress, cancer patients often cannot participate in psychotherapy such as MBIs, as traditional MBIs require patients to participate in classroom learning for several weeks (15,16). Physical fatigue and discomfort caused by the side effects of anticancer treatments, the stigma of cancer, limitations in transportation and the limited number of professional psychotherapists makes cancer patient access to MBIs difficult (17). MBIs delivered online have advantages as time-saving and labour-saving interventions with privacy for patients. Therefore, online MBIs are more popular with cancer patients compared with face-to-face interventions (18). Some studies have also confirmed the effectiveness of online MBIs. A meta-analysis by Spijkerman et al. summarized 15 randomized clinical trials (RCTs) and found that online MBIs have a positive impact on mental health outcomes (19). However, some of these trials included non-clinical participants, such as students or employees. A controlled trial of 64 cancer patients showed that online MBIs can effectively reduce stress (20). Another uncontrolled trial of 167 cancer patients showed that online MBIs significantly reduced fatigue and psychological problems (21).

Guided self-help (GSH) is a form of self-managed and standardized psychotherapy using books, manuals or media materials (such as the Internet, audio or video) with which participants can conduct psychotherapy independently at home. GSH can help participants complete interventions through supportive or promotional methods, which is different from other self-help methods (22,23). Some RCTs have demonstrated the beneficial effects of GSH-based cognitive behavioural therapy for psychological distress (24).

Several studies had investigated the efficacy of MBIs using self-help approaches (25). A meta-analysis by Cavanagh et al. including 15 studies demonstrated that guided self-help mindfulness-based interventions (GSH-MBIs) can benefit both healthy participants and participants with physical and psychological distress. However, in Cavanagh's review, only four studies evaluated the effect of GSH-MBIs, and no studies included cancer patients. Thus, the impact of GSH-MBIs on cancer patients is still unclear (26). Fish et al. conducted a systematic review of 10 studies on MBI support to participants through technical platforms. However, a definitive conclusion on the effectiveness of online MBIs cannot be drawn due to methodological differences in these studies (27). Toivonen et al. summarized 16 studies in a systematic review and showed that online MBIs are a practical choice for individuals with physical problems (28). Shao et al. found that GSH-MBIs for patients with breast cancer showed reductions in depression and sleep distress symptoms compared with a wait-list control group (25).

To summarize, GSH-MBIs may have potential therapeutic effects for cancer patients. The psycho-intervention effect on mental health of HCC patients is not clearly. Further randomized controlled studies of long-term intervention are needed to further investigate the effects of psycho-oncological intervention on HCC patients (3). To date, no study has evaluated the effects of GSH-MBIs on HCC patients. In addition, the mechanism of GSH-MBIs is still poorly understood.

Psychological flexibility refers to the ability to fully accept present thoughts, feelings and experiences with no evading, persisting or change behaviour to align with goals and values (29). The therapeutic activity of mindfulness is thought to occur through awareness and attention. Meditation training increases the ability for self-regulation of emotions and thoughts and improving psychological flexibility (30). Previous research has shown that MBIs can improve psychological flexibility and reduce perceived stress (31). However, the effect of GSH-MBIs on psychological flexibility and perceived stress and their role in reducing psychological distress are not yet clear.

In this study, we evaluated the impact of GSH-MBIs on the psychological symptoms of HCC patients. The primary objective was to investigate the effectiveness of 6-week GSH-MBIs on HCC patients immediately after the intervention and at follow-up timepoints. The first aim was to test the effectiveness of GSH-MBIs on primary outcome of psychological distress and secondary outcomes of quality of life and sleep quality. To better understand the mechanism of GSH-MBI interventions, the secondary objective was to investigate the mediator of psychological flexibility and perceived stress on these outcomes.

Methods

Trial design

From November 2019 to May 2021, the RCT was conducted at the First Hospital of Jilin University, China. Potential participants were identified through patient medical records. Patients were evaluated and screened; patients were invited to the study if they met the inclusion criteria. After providing informed consent, the subjects completed the baseline questionnaire (at T0) and then were randomly assigned to the IG or the waiting control group. Participants completed a questionnaire after 6 weeks of intervention (T1) and at the follow-ups at 1 month (T2) and 3 months (T3).

Randomization

After completing informed consent, screening, and baseline assessments, eligible participants were then randomized by an independent

research assistant who was not affiliated with the trial. Randomization was determined using Research Randomizer (version 4.0) (32), which generated a list of random numbers representing the participants and allocated them to the IG or the waiting control group. The outcome assessors were masked to the participant's group allocation.

Participants

The inclusion criteria were as follows: (i) age ≥ 18 years; (ii) diagnosis of HCC as an inpatient; (iii) no history of other malignancies; (iv) able to operate a smartphone and frequent WeChat (a widely used instant-messaging application in China) usage (>5 times per week); and (v) able to read, write and speak Chinese. The exclusion criteria were as follows: (i) a concurrent diagnosis of other tumour types or psychiatric distress; (ii) treatment with any psychotropic medications, such as antidepressants, antipsychotics, mood stabilizers, narcotics and benzodiazepines, any prescription for insomnia or any other antidepressive therapies during the study period; and (iii) previously received mindfulness intervention. The diagnosis of HCC was based on the European Association for the Study of the Liver (EASL) criteria and included histopathologic confirmation (33), positive lesion detection by at least two different imaging techniques, or positive lesion detection by one imaging technique combined with α-fetoprotein (AFP) > 400 ng/ml. The imaging techniques included transabdominal ultrasonography, angiography, computed tomography and magnetic resonance imaging.

Sample size

A sample size of 61 was selected to gain enough statistical power for subsequent analyses. This was based on previous post-intervention Hospital Anxiety and Depression Scale (HADS) scores of patients with cancer who received online mindfulness intervention (mean, 11.87; standard deviation [SD], 6.16) compared with those who had not received it (mean, 16.37; SD, 6.50). With 80% power and 5% type I error, we estimated that at least 44 participants were required in each group. To achieve these numbers, and allowing for a 27% dropout, we calculated that 61 participants were needed for each group (34).

Intervention

GSH-MBIs of 6-week duration were applied in the IG. The interventions were based on Mindfulness-Based Stress Reduction designed by Kabat-Zinn et al. and Mindfulness-Based Cognitive Therapy designed by Segal et al. (35,36). and was adapted for patients with HCC, which were developed by the research team. The team consisted of four experienced clinical psychologists. Interventions instructed principles and attitudes of mindfulness, guided the participants to focus on the present moment, and taught participants how to practice non-judgement during intense experiences, which may come from physical and psychological events or the external environment. Both guidance and home practice were used in the GSH-MBIs. The guidance included eight 20-minutes audio files. According to the physical condition of HCC patients, the guidance retained the core elements of mindfulness such as breath awareness, body scanning and awareness of pleasant and unpleasant events. At the same time, according to the main problems and demands of HCC patients, emotion (depression, anxiety) and symptom management (pain, insomnia) were added into the guidance. Home practice included three key exercises: breathing sense, body inspection and awareness of pleasant and unpleasant moods. Participants were required to conduct home practices based on the provided audio and practice 20 min each day and 5 days weekly for six consecutive weeks.

Before the start of the intervention, the psychologist scheduled a pre-intervention personal interview with each participant to introduce this intervention, explain training recommendations and answer any questions. Patients were asked to attempt this intervention before discharge and provide feedback to the instructor so that they could practice correctly. Each participant was provided with a manual containing instruction and guidance of this intervention and was asked to read it carefully to gain a better understanding of our intervention.

Participants were supervised and reminded to practice by the therapists everyday by WeChat, including personal guidance, answering questions and family practice feedback. After intervention, the participants completed one question: 'How many days have you listened to the audio and mindfulness practice during the intervention?' If participants had completed 20 days during the intervention period, they were considered adherent.

Waiting list group

Patients in the control group were given routine care, including health education and routine nursing guidance. After the study, these participants were introduced to the program and were provided with the audio and materials of the intervention.

Outcome measures

Demographics. Demographic and clinical characteristics, including basic demographic sociological information (age, gender, residence location, education level, occupation, spouse or absence, family economic condition) and clinical diseases (hepatic function classification) were collected.

Psychological distress. The HADS was used to measure psychological distress. The HADS was developed by Zigmond et al. (37) and is mainly used to assess the anxiety and depression of general patients. The HADS has been extensively validated in clinical practice (38) and is also suitable for cancer patients (39). The scale has 14 items, including the anxiety subscale (7 items) and the depression subscale (7 items). Each item is scored from 0 to 3 points, and the total score ranges from 0 to 42 points. A higher score indicates a higher anxiety and depression level. For the HADS scale, the test–retest reliability is 0.945, Cronbach's α is 0.879, and the criterion validity and construct validity are also good ($P < 0.001$) (40).

Sleep quality. Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI), which was compiled by Buysse et al. (41) and is currently the most widely used method for assessing sleep quality worldwide. The PSQI is used to assess the subjective sleep quality of an individual in the past month. It contains 19 items and is divided into seven dimensions: subjective sleep quality, time to fall asleep, sleep time, sleep efficiency, sleep disturbance, sleep medication use and daytime function. A higher score indicates a worse sleep quality. A total score >5 indicates poor sleep quality. For this scale, the test–retest reliability is 0.994, Cronbach's α is 0.845, and the discriminant validity and construct validity are also good ($P < 0.001$) (42).

Quality of life. Functional Assessment of Cancer Therapy-Hepatobiliary Carcinoma (FACT-Hep) was used to measure quality of life.

The FACT-Hep is a targeted measurement of the quality of life of patients with hepatobiliary carcinoma and is the most internationally recognized, comprehensive and commonly used assessment tool for the quality of life of patients with hepatobiliary cancer. It consists of 46 items and five dimensions. A higher score indicates a better quality of life of the patient. For this scale, the test–retest reliability is 0.330–0.953, Cronbach's α is 0.916, and the content validity and construct validity are also good ($P < 0.001$) (43).

Perceived stress. The Perceived Stress Scale (PSS) was used to assess the level of perceived stress. The scale, developed by Cohen et al. (44), includes 14 items to access the subjective stress of the individual; each item uses a 5-level scoring method (0–4 points). The total score is determined as the sum of the scores of each item. A higher score indicates a greater perceived stress. For the PSS scale, the test–retest reliability is 0.89, Cronbach's α is 0.78, and the discriminant validity and construct validity are also good ($P < 0.001$) (45).

Psychological flexibility. Psychological flexibility in this study was measured by the Acceptance and Action Questionnaire-second Edition (AAQ-II), with a total of seven items, that examined empirical avoidance, a negative emotion regulation strategy. A higher score indicated a higher empirical avoidance and lower psychological flexibility. For the AAQ-II scale, the test–retest reliability is 0.80, Cronbach's α is 0.88, and the criterion validity and construct validity are also good ($P < 0.01$) (46).

Ethical considerations. The protocol and principles of this study were conducted under the guidelines of the Declaration of Helsinki. This study was approved by the Ethics Committee of the School of Nursing of Jilin University (ID#2019112001) and was registered in the Chinese Clinical Trial Registry (ChiCTR1900027976). All patients provided written informed consent prior to the study and were allowed to stop participating at any time.

Statistical analysis

The distribution of data was tested using the Shapiro–Wilk test, where continuous variables that conformed to the normal distribution were described with means and SD, and those that did not conform to the normal distribution were described with medians and quartiles. Frequency and percentage were used for categorical variables. Baseline characteristics of the intervention and control groups were compared using independent t-tests, nonparametric tests or χ^2 test. To measure the outcomes over time, generalized estimated equation (GEE) models with an unstructured correlation matrix were fitted. The threshold for significance was set at $\alpha = 0.05$. Intention-to-treat analysis method was used to analyse the data so that all randomly assigned subjects remained in the assigned corresponding group; the data of the missing part were analysed by the last observation value carry forward method. Statistical analysis was conducted using SPSS, version 22.0 for Windows (IBM Corporation).

Results

Baseline characteristics of participants

Among the 332 patients that were initially recruited, 122 patients met the eligibility criteria and agreed to participate in the study. Among the 122 patients, 61 patients were randomized into the IG and 61 were randomized into the control group (CG) At the end of the intervention, 15 were lost in the IG and 13 were lost in the CG, leaving 93 participants that completed the assessment. There was no statistically significant difference in the lost participants between the two groups ($P > 0.05$), as shown in Figure 1.

The age range of the participants in the overall group was 36–70 years old (average ± SD, 55.69 ± 8.30 years). The demographic and clinical data of the IG were not statistically different from those of the CG ($P > 0.05$), as shown in Table 1.

The effect of the intervention on outcomes

The home practice time in the IG ranged from 10 to 32 days (22.35 ± 4.11 days). Participants that practiced for 21 days were defined as showing persistence. The compliance rate of this study was 74.2%. Comparisons of outcomes between the intervention and CGs are presented in Table 2. Figure 2 shows a visual representation of the changing trend. Regarding the results from the GEE analysis results, the interaction effects of group-by-time were significant on psychological distress and sleep quality ($P < 0.001$). Regarding the results of intragroup comparisons, we could see that in the IG, the scores of HADS and PSQI were significantly lower at T1 (HADS: $P < 0.001$; PSQI: $P < 0.001$), T2 (HADS: $P < 0.001$; PSQI: $P < 0.001$) as well as T3 (HADS: $P < 0.001$; PSQI: $P = 0.007$) compared with those at the baseline; the FACT-Hep scores were markedly higher compared with baseline at T1 ($P = 0.015$) and T2 ($P = 0.044$); whereas in the CG, the scores at T1,T2 andT3 were not significantly different from those at the baseline for all the outcomes ($P > 0.051$). Intergroup comparisons at T1, displayed a significantly lower HADS score in the IG (11.97 ± 2.88) compared with the CG (13.74 ± 4.73; $P = 0.012$), and PSQI score in IG (9.11 ± 2.85) compared with CG (10.52 ± 3.02; $P = 0.007$). However, FACT-Hep score (IG: 123.45 ± 12.91; CG: 121.29 ± 15.59; $P = 0.402$), was not significantly different between the two groups. At T2, the trend persisted with significantly lower HADS scores in IG compared with CG (IG: 12.03 ± 2.73; CG: 13.85 ± 4.50; $P = 0.006$), and PSQI scores in IG compared with CG (IG: 9.03 ± 2.83; CG: 10.54 ± 2.95; $P = 0.004$). Like T1, at T2, FACT-Hep scores (IG: 123.38 ± 13.06; CG: 120.62 ± 15.31; $P = 0.281$), were still remained insignificant between the two groups at T2. At T3, the trend persisted with significantly lower HADS scores in IG compared with CG (IG: 11.95 ± 2.85; CG: 14.11 ± 4.26; $P = 0.001$), and PSQI scores in IG compared with CG (IG: 9.21 ± 2.67; CG: 10.56 ± 2.71; $P = 0.005$). Like T1 and T2, at T3, FACT-Hep scores (IG: 123.18 ± 12.25; CG: 120.18 ± 14.76; $P = 0.218$), were still remained insignificant between the two groups at T3.

The effect of the intervention on mediators

The GEE model was used to analyse the influence of the intervention on psychological flexibility and perceived stress. The differences of scores at different times were significant ($P < 0.05$). The results showed that the intervention significantly improved psychological flexibility (β, −2.639; 95% CI, −4.110, −1.169) and reduced perceived stress (β, −2.066; 95% CI, −3.631, −0.500).

Mediation analysis

In this study the causal step model proposed by Baron and Kenny was followed to test the mediation effect (47). Firstly, we tested whether the effect of the intervention on the outcome variable (psychological distress and sleep quality) was significant. GEE analysis showed that the intervention reduced psychological distress as well as sleep problems; then we tested whether the effect of the intervention

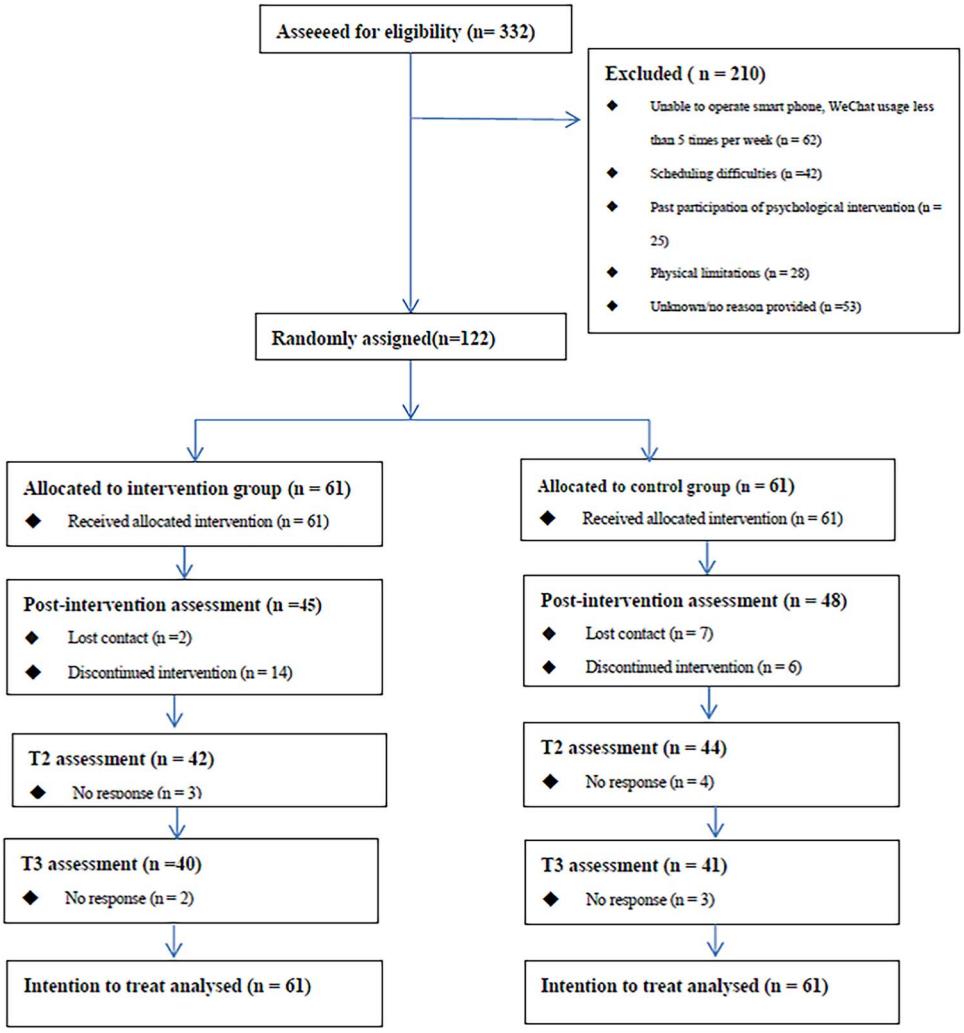

Figure 1. Flowchart showing recruitment and dropout of participants.

on the mediating variable (psychological flexibility and perceived stress) was significant, GEE analysis showed that the intervention reduced empirical avoidance and perceived stress. Finally, the effect of intervention and mediating variables on outcome variables was considered in the model simultaneously, and we tested whether the effect of the mediating variable on outcome variables was significant. If it was significant, it indicated that the mediation effect is significant. At the same time, we tested whether the intervention has a significant effect on the outcome variable after controlling for the mediating variables.

We added time, group and their interaction, as well as mediator variables, to the model, and the results showed that the effect of psychological flexibility and perceived stress on psychological distress was significant. The effect of intervention on psychological distress was still significant after controlling for the mediating variables, indicating a mediating role for psychological flexibility and perceived stress on psychological distress. The results also showed that the effect of perceived stress on sleep quality was significant. The effect of intervention on psychological distress was non-significant after controlling for the mediating variables, indicating a complete mediating role for perceived stress on psychological distress (Table 3).

Discussion

To our knowledge, this is the first randomized controlled trial of GSH-MBIs in HCC patients. Our results showed that GSH-MBIs significantly reduced the severity of psychological distress and improved sleep quality in HCC patients. The 1-month and 3-month follow-up data showed that the improvements in terms of depression and sleep quality in the IG was continued at 1 month and 3 months after treatment. An improvement of the quality of life after the intervention was observed, but without statistical significance, which might be related to the changes of the quality of life of cancer patients reported in the previous study (34). The mediation analysis revealed the possible psychological mechanism of GSH-MBIs. The results suggested that changes in psychological flexibility and perceived stress in HCC patients mediate the changes in psychological distress and sleep quality after the intervention.

The post-intervention effect sizes for psychological distress found in our study are smaller than the effect in another previous study of online MBIs in cancer patients (34). When comparing the results, between study differences in participant selection procedures should be noted. Although relatively high-distress level cutoffs were applied in the previous study, HADS scores $\geq$11, the present study used a lower cutoff, which could have introduced floor effects. One solution

Table 1. Demographics and medical characteristics of participants at baseline, $n = 122$

Variables	No.(%)		*t-test* or chi-square test	*P*
	Intervention Group, $n = 61$	Control Group, $n = 61$		
Age:	54.36 ± 8.46	57.02 ± 8.00	−1.78	0.077
Mean ± SD, years				
Gender	46(75.4)	48(78.7)	0.19	0.67
Male	15(24.6)	13(21.3)		
Female				
Relationship status	53(86.9)	55(90.2)	0.323	0.57
Married				
Divorced/widowed	8(13.1)	6(9.8)		
Education	12(19.7)	11(18.0)	0.87	0.83
Primary school or below	28(45.9)	28(45.9)		
Junior high school	16(26.2)	14(23.0)		
Senior high school	5(8.2)	8(13.1)		
College or higher				
Residence	32(52.5)	36(59.0)	0.53	0.466
City	29(47.5)	25(41.0)		
Noncity				
Employment state	29(47.5)	33(54.1)	0.525	0.469
Employed	32(52.5)	28(45.9)		
Unemployed				
Average monthly income	29(47.5)	22(36.1)	1.69	0.43
≤4000yuan	24(39.3)	30(49.2)		
4001–8000yuan	8(13.1)	9(14.8)		
>8000yuan				
Child-Pugh	47(77.0)	40(65.6)	2.04	0.36
Class A	13(21.3)	19(31.1)		
Class B	1(1.6)	2(3.3)		
Class C				

for including the patients most likely to benefit could be a more comprehensive screening procedure or a higher cutoff when screening patients.

Our research further verified the effects of GSH-MBIs on cancer patients (17,25,34). To our knowledge, it is the first study to evaluate the effects of GSH-MBIs on HCC patients. Approximately 50% of HCC patients suffered from depression (48), and this study provides a new method to reduce the depression of HCC patients. Compared with traditional group-based MBIs, GSH-MBIs are more suitable in developing countries with limited psychology resources. GSH-MBIs can provide HCC patients with audio and files for mindfulness learning and practice through WeChat, and at the same time, professionals can keep in touch with patients through online platforms. Compared with face-to-face methods, GSH-MBIs greatly reduce medical expenses (49). HCC cancer patients generally suffer from physical symptoms such as fatigue and pain, HCC patients often suffer from physical symptoms such as fatigue and pain, as well as limited mobility (50), this method has increased the feasibility of obtaining mental health care and ensured the privacy of patients.

The loss rate during follow-up in this study (34%) was higher than other RCTs of face-to-face mindfulness interventions (34,51). Among the study dropouts, 43% of the participants responded having no time to complete courses and practice because of work and housework, 24% did not give any reason, 14% did not continue because of physical discomfort and fatigue, 10% of the drop-out participants thought that the course content had no effects and 10% thought that the evaluation was tedious. Based on these reasons, we concluded that the obstacles to completing this study were mainly from other daily tasks, physical discomfort and the burden of assessment, rather than the course content or duration. These observations suggest that GSH-MBIs are suitable for patients with a higher willingness to participate, free time and relatively mild disease.

We also investigated the mediating role of GSH-MBIs and showed that psychological flexibility and perceived stress influenced the symptoms of psychological distress and sleep quality. The findings demonstrated that psychological flexibility was an important mediator of stress and emotion in cancer patients (31,52). There is empirical avoidance with low psychological flexibility, which is characterized by trying to change or avoid unwanted thoughts and feelings. The usual response to negative thoughts and feelings is avoidance (53). Mindfulness practice improves participants' concentration and awareness, self-regulation of pain, mental flexibility and reduced psychological pressure (54).

Limitations

This study has several limitations, First, the collected data are all self-reports, and the accuracy of reports could not be confirmed. In future studies, more advanced techniques will be used to record the practice time of participants. Second, these samples were recruited in a tertiary hospital, which limited the conclusions on the effects

Table 2. Model effect estimation using generalized estimated equations based on the intention-to-treat sample, $n = 122$

Outcome	Intervention Group	Control Group	Intergroup comparisons		Linear mixed-effects model (*P*-value)			Change from baseline (95% CI)	
			Effect Size	95% CI	Group	Time	Group×time	Intervention Group	Control Group
HADS					0.039*	0.009**	<0.001***		
T0	13.89 ± 4.67	13.64 ± 4.65	0.05	0.25(−1.39, 1.89)				—	—
T1	11.97 ± 2.88	13.74 ± 4.73	–0.45	−1.77(−3.15, −0.39)*				−1.92(−2.82, −1.02)***	0.10(−0.44, 0.64)
T2	12.03 ± 2.73	13.85 ± 4.50	–0.49	−1.82(−3.13, −0.51)**				−1.85(−2.82, −0.89)***	0.21(−0.28, 0.71)
T3	11.95 ± 2.85	14.11 ± 4.26	–0.60	−2.16(−3.44, −0.89)**				−1.93(−2.82, −1.04)***	0.48(−0.05, 1.00)
FACT-Hep					0.393	0.054	0.214		
T0	121.57 ± 16.16	120.78 ± 15.53	0.05	0.79(−4.79, 6.37)				—	—
T1	123.45 ± 12.91	121.29 ± 15.59	0.15	2.15(−2.88, 7.19)				1.88(0.36, 3.39)*	0.51(−0.47, 1.49)
T2	123.38 ± 13.06	120.62 ± 15.31	0.19	2.75(−2.25, 7.76)				1.80(0.05, 3.56)*	−0.16(−1.09, 0.77)
T3	123.18 ± 12.25	120.18 ± 14.76	0.22	3.00(−1.77, 7.78)				1.61(−0.17, 3.39)	0.0.60(−1.80, 0.60)
PSQI					0.019*	0.005**	<0.001***		
T0	9.74 ± 3.31	10.36 ± 3.29	–0.19	−0.63(−1.79, 0.53)				—	—
T1	9.11 ± 2.85	10.52 ± 3.02	–0.55	−1.41(−2.44, −0.38)**				−0.62(−0.88, −0.36)***	0.16(0.00, 0.32)
T2	9.03 ± 2.83	10.54 ± 2.95	–0.60	−1.51(−2.52, −0.49)**				−0.70(−0.97, −0.44)***	0.18(−0.06, 0.41)
T3	9.21 ± 2.67	10.56 ± 2.71	–0.57	−1.34(−2.29, −0.40)**				−.52(−0.91, −0.14)**	0.19(−0.16, 0.55)

Note: The scores of scales were presented as means ± standard deviations.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

Abbreviations: HADS, Hospital Anxiety and Depression Scale; FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary Carcinoma; PSQI, Pittsburgh Sleep Quality Index; T0, time 0 (baseline); T1, time 1 (post-intervention); T2, time 2 (1-month follow-up); T3, time 3 (3-month follow-up).

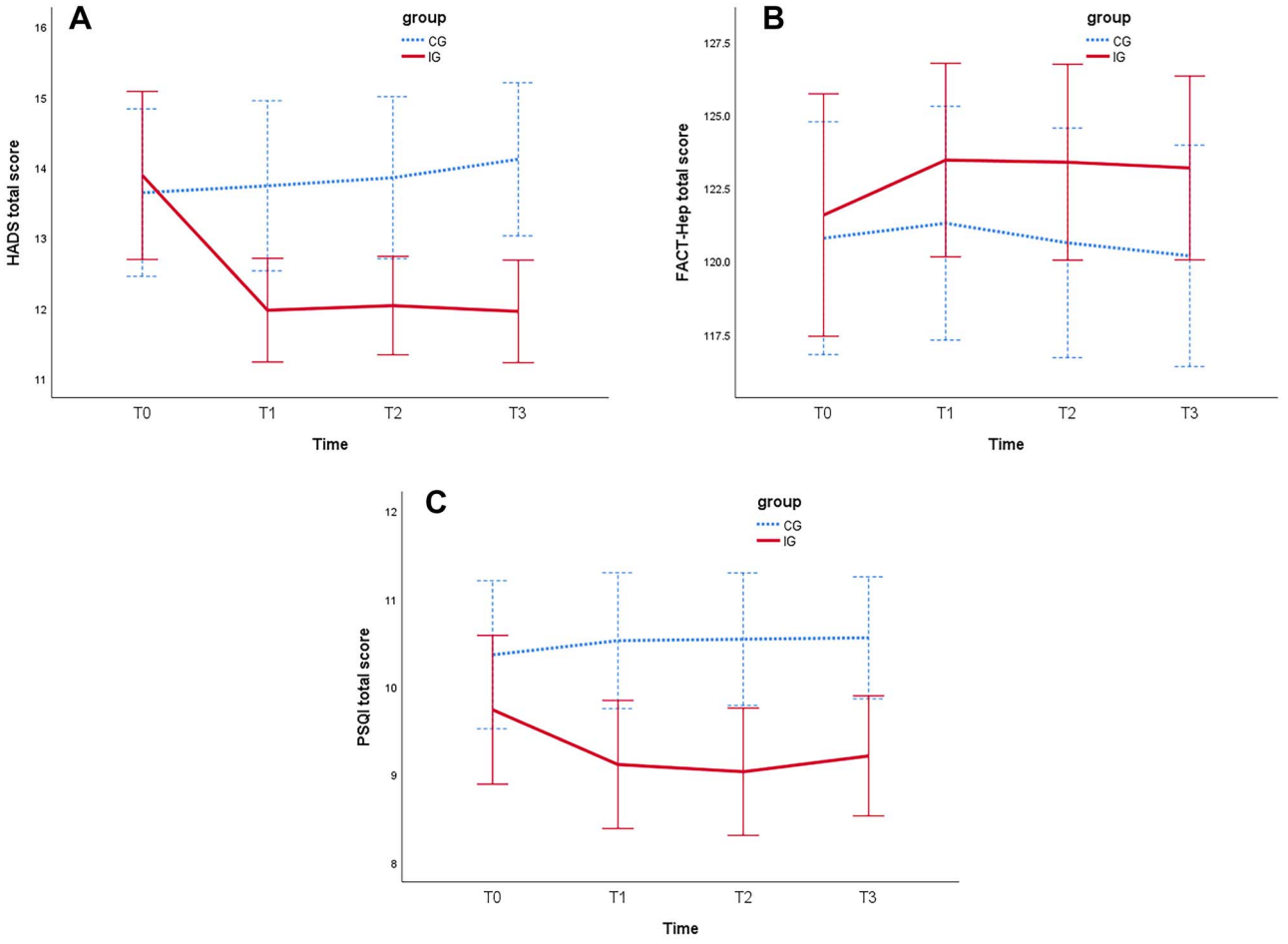

Figure 2. The change trends of outcomes in intervention and control groups over time. Abbreviations: CG, Control Group; IG, Intervention Group; HADS, Hospital Anxiety and Depression Scale; FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary Carcinoma; PSQI, Pittsburgh Sleep Quality Index. T0, time 0 (baseline); T1, time 1 (post-intervention); T2, time 2 (1-month follow-up); T3, time 3 (3-month follow-up). Error bars represent 95% confidence intervals.

Table 3. Model effect estimation using generalized estimated equations, $n = 122$

Outcome	waldχ^2	Degree of freedom	*P*	Difference of marginal means (95% CI)
HADS				
Group	0.01	1	0.918	0.04(−0.71, 0.79)
Time	0.59	1	0.443	0.20(−0.31, 0.71)
Time×group	10.05	1	0.002	−1.66(−2.68, −0.63)
Psychological flexibility	13.53	1	<0.001	0.15(0.07, 0.23)
Perceived stress	64.01	1	<0.001	0.28(0.21, 0.35)
PSQI				
Group	2.30	1	.129	0.67(−0.20, 1.54)
Time	0.09	1	0.763	0.03(−0.17, 0.23)
Time×group	2.13	1	0.144	−0.29 (−0.69, 0.10)
Psychological flexibility	3.09	1	0.079	0.07(−0.01, 0.14)
Perceived stress	20.103	1	<0.001	0.15(0.09, 0.22)

Abbreviations: HADS, Hospital Anxiety and Depression Scale; PSQI, Pittsburgh Sleep Quality Index.

and mechanisms of the intervention. Third, this study did not collect information on the time that the participants were in contact with researchers and with social exposure. Future research should consider social support and other factors. Finally, a high drop-out rate was observed in this study, especially at the beginning of intervention, which could indicate insufficient recruitment and information procedures. It could be that this type of intervention does not fully meet the needs, expectations and skills of the target population. Participants completed baseline assessments prior to randomization, but additional in-depth assessment of motivation and

internet literacy prior to intervention start could have been relevant. Intervention dropout could possibly be improved by the delivery mode of GSH-MBIs.

Conclusion

In summary, GSH-MBIs can significantly improve the psychological distress of HCC patients, which was mediated by psychological flexibility and perceived stress. Simultaneously, we also found that GSH-MBIs can improve the sleep quality of HCC patients. Using easy and innovative technology, participants can easily learn and practice, and professionals can provide support. The study verified the advantages of GSH-MBIs, such as high efficiency, low cost, low intensity, easy access and anonymity, and also proved its effects on HCC patients, and provided for larger scale experimental research on GSH-MBIs in the treatment of HCC patients.

Acknowledgements

We would like to thank all participants and researchers for their cooperation. No funding was received for this study.

Conflicts of interest statement

None declared.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
2. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2021;7:6.
3. Graf J, Stengel A. Psychological burden and psycho-oncological interventions for patients with hepatobiliary cancers-a systematic review. *Front Psychol* 2021;12:662777.
4. Zhong GC, Liu Y, Chen N, et al. Reproductive factors, menopausal hormone therapies and primary liver cancer risk: a systematic review and dose-response meta-analysis of observational studies. *Hum Reprod Update* 2016;23:126–38.
5. Wang Y, O'Connor M, Xu Y, Liu X. Symptom clusters in Chinese patients with primary liver cancer. *Oncol Nurs Forum* 2012;39:E468–79.
6. Küchler T, Bestmann B, Rappat S, Henne-Bruns D, Wood-Dauphinee S. Impact of psychotherapeutic support for patients with gastrointestinal cancer undergoing surgery: 10-year survival results of a randomized trial. *J Clin Oncol* 2007;25:2702–8.
7. Steel JL, Nadeau K, Olek M, Carr BI. Preliminary results of an individually tailored psychosocial intervention for patients with advanced hepatobiliary carcinoma. *J Psychosoc Oncol* 2007;25:19–42.
8. Deng G, Cassileth B. Complementary or alternative medicine in cancer care-myths and realities. *Nat Rev Clin Oncol* 2013;10:656–64.
9. Elkins G, Fisher W, Johnson A. Mind-body therapies in integrative oncology. *Curr Treat Options Oncol* 2010;11:128–40.
10. Zainal NZ, Booth S, Huppert FA. The efficacy of mindfulness-based stress reduction on mental health of breast cancer patients: a meta-analysis. *Psychooncology* 2013;22:1457–65.
11. Rouleau CR, Garland SN, Carlson LE. The impact of mindfulness-based interventions on symptom burden, positive psychological outcomes, and biomarkers in cancer patients. *Cancer Manag Res* 2015;7:121–31.
12. Cillessen L, Johannsen M, Speckens AEM, Zachariae R. Mindfulness-based interventions for psychological and physical health outcomes in cancer patients and survivors: a systematic review and meta-analysis of randomized controlled trials. *Psychooncology* 2019;28:2257–69.
13. Xunlin NG, Lau Y, Klainin-Yobas P. The effectiveness of mindfulness-based interventions among cancer patients and survivors: a systematic review and meta-analysis. *Support Care Cancer* 2020;28:1563–78.
14. Piet J, Würtzen H, Zachariae R. The effect of mindfulness-based therapy on symptoms of anxiety and depression in adult cancer patients and survivors: a systematic review and meta-analysis. *J Consult Clin Psychol* 2012;80:1007–20.
15. Wang JW, Shen Q, Ding N, et al. A qualitative exploration of the unmet psychosocial rehabilitation needs of cancer survivors in China. *Psychooncology* 2016;25:905–12.
16. Jacobsen PB, Jim HS. Psychosocial interventions for anxiety and depression in adult cancer patients: achievements and challenges. *CA Cancer J Clin* 2008;58:214–30.
17. Zernicke KA, Campbell TS, Speca M, McCabe-Ruff K, Flowers S, Carlson LE. A randomized wait-list controlled trial of feasibility and efficacy of an online mindfulness-based cancer recovery program: the eTherapy for cancer applying mindfulness trial. *Psychosom Med* 2014;76:257–67.
18. Brebach R, Sharpe L, Costa DS, Rhodes P, Butow P. Psychological intervention targeting distress for cancer patients: a meta-analytic study investigating uptake and adherence. *Psychooncology* 2016;25:882–90.
19. Spijkerman MP, Pots WT, Bohlmeijer ET. Effectiveness of online mindfulness-based interventions in improving mental health: a review and meta-analysis of randomised controlled trials. *Clin Psychol Rev* 2016;45:102–14.
20. Zernicke KA, Campbell TS, Speca M, McCabe-Ruff K, Flowers S, Dirkse DA, Carlson LE. The eCALM trial-eTherapy for cancer appLying mindfulness: online mindfulness-based cancer recovery program for underserved individuals living with cancer in Alberta: protocol development for a randomized wait-list controlled clinical trial. *BMC Complement Altern Med* 2013;13:34.
21. Bruggeman-Everts FZ, Wolvers MDJ, van de Schoot R, Vollenbroek-Hutten MMR, van der Lee ML. Effectiveness of two web-based interventions for chronic cancer-related fatigue compared to an active control condition: results of the "fitter na Kanker" randomized controlled trial. *J Med Internet Res* 2017;19:e336.
22. Delgadillo J. Guided self-help in a brave new world. *Br J Psychiatry* 2018;212:65–6.
23. Cuijpers P, Donker T, van Straten A, Li J, Andersson G. Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety distresss? A systematic review and meta-analysis of comparative outcome studies. *Psychol Med* 2010;40:1943–57.
24. Coull G, Morris PG. The clinical effectiveness of CBT-based guided self-help interventions for anxiety and depressive distresss: a systematic review. *Psychol Med* 2011;41:2239–52.
25. Shao D, Zhang H, Cui N, Sun J, Li J, Cao F. The efficacy and mechanisms of a guided self-help intervention based on mindfulness in patients with breast cancer: a randomized controlled trial. *Cancer* 2021;127:1377–86.
26. Cavanagh K, Strauss C, Forder L, Jones F. Can mindfulness and acceptance be learnt by self-help?: a systematic review and meta-analysis of mindfulness and acceptance-based self-help interventions. *Clin Psychol Rev* 2014;34:118–29.
27. Fish J, Brimson J, Lynch S. Mindfulness interventions delivered by technology without facilitator involvement: what research exists and what are the clinical outcomes? *Mindfulness (N Y)* 2016;7:1011–23.
28. Toivonen KI, Zernicke K, Carlson LE. Web-based mindfulness interventions for people with physical health conditions: systematic review. *J Med Internet Res* 2017;19:e303.
29. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. *Behav Res Ther* 2006;44:1–25.
30. Bishop SR. What do we really know about mindfulness-based stress reduction? *Psychosom Med* 2002;64:71–83.
31. Lengacher CA, Gruss LF, Kip KE, et al. Mindfulness-based stress reduction for breast cancer survivors (MBSR(BC)): evaluating mediators of psychological and physical outcomes in a large randomized controlled trial. *J Behav Med* 2021;44:591–604.
32. Urbaniak GC, Plous S. *Research Randomizer, version 4.0 [software program]*. andomizer.org, 2013. http://www.randomizer.org/ (6 March 2016, date last accessed).

33. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the liver. *J Hepatol* 2001;35:421–30.
34. Compen F, Bisseling E, Schellekens M, Donders R, Carlson L, van der Lee M, Speckens A. Face-to-face and internet-based mindfulness-based cognitive therapy compared with treatment as usual in reducing psychological distress in patients with cancer: a Multicenter randomized controlled trial. *J Clin Oncol* 2018;36:2413–21.
35. Kabat-Zinn J, Massion AO, Kristeller J, et al. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety distresss. *Am J Psychiatry* 1992;149:936–43.
36. Teasdale JD, Segal ZV, Williams JM, Ridgeway VA, Soulsby JM, Lau MA. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *J Consult Clin Psychol* 2000;68:615–23.
37. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
38. Edmondson D, Gamboa C, Cohen A, et al. Association of posttraumatic stress distress and depression with all-cause and cardiovascular disease mortality and hospitalization among Hurricane Katrina survivors with end-stage renal disease. *Am J Public Health* 2013;103:e130–7.
39. Akechi T, Okuyama T, Sugawara Y, Shima Y, Furukawa TA, Uchitomi Y. Screening for depression in terminally ill cancer patients in Japan. *J Pain Symptom Manage* 2006;31:5–12.
40. Zhenxiao S, Huaxue L, Linying J, et al. Reliability and validity of hospital anxiety and depression scale. *Chin J Clin* 2017;11:198–201.
41. Buysse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
42. Taoying L, Yan L, Ping X, et al. Analysis on reliability and validity of the Pittsburgh sleep quality index. *Chongqing Med* 2014;43:260–3.
43. Zhu Z, Lang Q, Chen Z, Li DT, Ling CQ. Evaluation of Chinese version of the functional assessment of cancer therapy-hepatobiliary questionnaire. *J Chin Integr Med* 2008;6:341–5.
44. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24:385–96.
45. Qinglong D, Ruoyu H, Jiwei W, et al. Validity and reliability of the perceived stress scale among cancer survivors. *Chin Ment Health J* 2018;32:15–20.
46. Jing C, Yang J, Zhuo-Hong Z. Reliability and validity of the Chinese version of the acceptance and action questionnaire-second edition (AAQ-II) in college students. *Chin Ment Health J* 2013;27:873–7.
47. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;51:1173–82.
48. Jia Y, Zhang W, You S, Li M, Lei L, Chen L. A nomogram for predicting depression in patients with hepatocellular carcinoma: an observational cross-sectional study. *Int J Psychiatry Clin Pract* 2019;23:273–80.
49. Russell L, Ugalde A, Milne D, Austin D, Livingston PM. Digital characteristics and dissemination indicators to optimize delivery of internet-supported mindfulness-based interventions for people with a chronic condition: systematic review. *JMIR Ment Health* 2018;5:e53.
50. Patel N, Maher J, Lie X, et al. Understanding the patient experience in hepatocellular carcinoma: a qualitative patient interview study. *Qual Life Res* 2021. https://doi.org/10.1007/s11136-021-02903-4.
51. Zernicke KA, Campbell TS, Blustein PK, Fung TS, Johnson JA, Bacon SL, Carlson LE. Mindfulness-based stress reduction for the treatment of irritable bowel syndrome symptoms: a randomized wait-list controlled trial. *Int J Behav Med* 2013;20:385–96.
52. Labelle LE, Campbell TS, Faris P, Carlson LE. Mediators of mindfulness-based stress reduction (MBSR): assessing the timing and sequence of change in cancer patients. *J Clin Psychol* 2015;71:21–40.
53. Hayes SC, Wilson KG, Gifford EV, Follette VM, Strosahl K. Experiential avoidance and behavioral disorders: a functional dimensional approach to diagnosis and treatment. *J Consult Clin Psychol* 1996;64:1152–68.
54. Lindsay EK, Creswell JD. Mechanisms of mindfulness training: monitor and acceptance theory (MAT). *Clin Psychol Rev* 2017;51:48–59.