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The effect of mind-mapping health interventions on nutritional and renal parameters during radiotherapy in patients with nasopharyngeal carcinoma

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► ***Original article***

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ABSTRACT

Background: This study evaluated the impact of mind-mapping health interventions on nutritional status, renal function, and inflammatory markers in nasopharyngeal carcinoma (NPC) patients undergoing radiotherapy. ***Materials and Methods:*** A retrospective analysis was conducted on 120 NPC patients treated with intensity-modulated radiotherapy (66-70 Gy, 2 Gy/fraction over 6-7 weeks) at the First Affiliated Hospital of Harbin Medical University (2022-024). Patients were assigned to either standard care (n=60) or mind-mapping intervention (n=60). The intervention incorporated structured education on nutrition, symptom control, behavioral management, and renal monitoring using visual mind maps. Nutritional indicators [standardized dietary energy intake (NDEI), standardized dietary protein intake (NDPI), body mass index (BMI), mid-arm muscle circumference (MAMC)], renal parameters [serum creatinine (Scr), blood urea nitrogen (BUN), glomerular filtration rate (GFR)], and inflammatory markers [C-reactive protein (CRP), interleukin-6 (IL-6)] were assessed at baseline and 2, 4, and 6 weeks. Radiotherapy-related complications were recorded. ***Results:*** The intervention group demonstrated a significantly lower incidence of complications (8.3% vs. 21.7%, P=0.031). Nutritional indices improved markedly at 6 weeks (NDEI: 140.5±21.2 vs. 125.4±20.1 kJ/kg/day; NDPI: 1.42±0.33 vs. 1.25±0.27 g/kg/day; P<0.05). Renal function was preserved with reduced Scr (60.1±12.0 vs. 70.2±13.2 µmol/L) and BUN, and higher GFR (P<0.05). CRP (6.0±1.8 vs. 8.2±2.1 mg/L) and IL-6 (9.2±2.7 vs. 13.0±3.2 pg/mL) were significantly lower in the intervention group. ***Conclusion:*** Mind-mapping interventions effectively reduce radiotherapy-related complications, enhance nutrition, preserve renal function, and mitigate inflammation in NPC patients. Their integration into clinical practice may improve radiotherapy outcomes.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor arising from the epithelial lining of the nasopharynx and is especially prevalent in southern China and Southeast Asia, where it represents a significant public health burden [1, 2]. Its etiology is multifactorial, with Epstein-Barr virus (EBV) infection, genetic susceptibility, and environmental exposures identified as major contributors [3]. Radiotherapy, frequently combined with chemotherapy, remains the cornerstone of treatment due to the tumor's high radiosensitivity and the anatomic challenges associated with surgical resection [4, 5]. Advances in intensity-modulated radiotherapy (IMRT) have improved local control and survival rates, yet treatment-related toxicities remain common and problematic [6].

Radiotherapy can induce acute and chronic side effects such as oral mucositis, dysphagia, xerostomia, and dermatitis, which compromise nutritional intake, impair renal function, and provoke systemic inflammatory responses [7, 8]. Malnutrition and treatment-related renal stress are strongly associated with poorer tolerance to therapy, higher complication rates, and reduced quality of life. Elevated biomarkers, including serum creatinine (Scr), blood urea nitrogen (BUN), and inflammatory mediators such as C-reactive protein (CRP) and interleukin-6 (IL-6), further predict adverse outcomes in NPC patients [9, 10].

Conventional supportive care for NPC patients largely emphasizes symptomatic relief and basic dietary counseling. However, this fragmented approach often fails to address the complex and interrelated challenges patients face during radiotherapy [11, 12]. Mind-mapping, a structured visual tool for organizing information, has been successfully applied in medical education, chronic disease management, and patient self-care to improve comprehension and adherence [13]. By integrating nutritional management, symptom control, behavioral guidance, and renal monitoring into a single, accessible framework, mind-mapping may provide a more comprehensive and patient-centered strategy.

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To our knowledge, this is the first study to evaluate mind-mapping health interventions in NPC patients receiving radiotherapy. Unlike prior research focusing on isolated interventions such as nutritional supplementation or symptom management, our study examines an integrated, multidisciplinary approach. We hypothesize that mind-mapping interventions can enhance nutritional outcomes, protect renal function, and mitigate systemic inflammation, thereby improving the overall therapeutic experience and prognosis for NPC patients.

MATERIALS AND METHODS

Study population

A total of 120 patients with biopsy-confirmed nasopharyngeal carcinoma (NPC) were enrolled. Patients were assigned to either a control group (n=60), which received standard care, or an intervention group (n=60), which received mind-mapping health interventions. Both groups were comparable in age, sex, body mass index (BMI), tumor stage according to the TNM classification, and radiotherapy duration ($P>0.05$). Eligible patients were required to have a confirmed NPC diagnosis, be scheduled for intensity-modulated radiotherapy (IMRT), have an expected survival of more than one year, and demonstrate normal cognitive and communication abilities. Exclusion criteria included pre-existing renal disease, severe comorbidities such as heart failure or liver dysfunction, previous radiotherapy or chemotherapy within six months, or inability to comply with the study protocol.

Radiotherapy protocol

Radiotherapy was delivered using an Elekta Infinity linear accelerator (Elekta AB, Stockholm, Sweden). Patients received IMRT with a prescribed total dose of 66–70 Gy in 2.0 Gy fractions, five fractions per week, over a course of six to seven weeks. The planning target volume encompassed the nasopharyngeal tumor, involved lymph nodes, and a 5-mm margin, while organs at risk such as the parotid glands, spinal cord, and brainstem were spared according to Radiation Therapy Oncology Group (RTOG) guidelines. Treatment planning was performed with the Monaco Treatment Planning System (Elekta AB, Sweden, v5.11).

Pre-radiotherapy simulation was carried out using a Siemens SOMATOM Definition AS scanner (Siemens Healthineers, Erlangen, Germany). Intravenous contrast enhancement was achieved with iopamidol (Iopamiron®, Bayer Healthcare, Germany). Weekly cone-beam CT was used to ensure setup accuracy throughout the treatment period. Patients with stage III–IV disease additionally received concurrent cisplatin chemotherapy (40 mg/m^2 weekly, Pfizer, USA).

Intervention protocols

Patients in the control group received standard care, which included dietary counseling to maintain an intake of 30-35 kcal/kg/day and 1.2-1.5 g/kg/day protein, oral care, hydration support, and general management of radiotherapy-related side effects. Oncology nurses conducted weekly follow-up sessions to address concerns.

Patients in the intervention group received a structured mind-mapping program developed using MindManager software (Mindjet, USA, v20.1). The mind maps integrated four key domains: nutritional management, symptom control, behavioral education, and renal monitoring. Nutritional interventions were individualized and adapted for dysphagia, with high-calorie liquid supplements (Boost®, Abbott Laboratories, USA) and sodium restriction (2–3 g/day; Morton Salt, USA). Symptom control included oral rinses with chlorhexidine (Colgate-Palmolive, USA) and pain management with ibuprofen (Advil®, Pfizer, USA). Patients were educated to recognize and report early symptoms such as mucositis or xerostomia. Renal monitoring involved weekly evaluations of serum creatinine, blood urea nitrogen (BUN), and glomerular filtration rate (GFR). These interventions were delivered daily by trained oncology nurses for 20–30 minutes and adjusted weekly according to patient progress.

Outcome measures

Clinical evaluations were performed at baseline (prior to radiotherapy simulation) and at 2, 4, and 6 weeks after the initiation of radiotherapy. Radiotherapy-related complications, including mucositis, dysphagia, xerostomia, and dermatitis, were documented, and total incidence rates were calculated. Nutritional status was assessed by measuring standardized dietary energy intake (NDEI, kJ/kg/day), standardized dietary protein intake (NDPI, g/kg/day), BMI, and mid-arm muscle circumference (MAMC, cm), with MAMC measured using a Seca 201 tape (Seca GmbH, Hamburg, Germany). Renal function was determined by analyzing fasting venous blood samples for serum creatinine and BUN using the Beckman Coulter AU5800 analyzer (Beckman Coulter, USA), while GFR was calculated with the CKD-EPI equation. Inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), were measured with commercial ELISA kits (Human CRP Quantikine ELISA Kit and Human IL-6 Quantikine ELISA Kit, R&D Systems, USA) and analyzed on a Bio-Rad iMark Microplate Reader (Bio-Rad Laboratories, USA).

Ethical considerations

This retrospective study was conducted at the Oncology Department, First Affiliated Hospital of Harbin Medical University, Harbin, China, between January 2022 and January 2024. Ethical approval was granted by the Ethics Committee of the First Affiliated

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Hospital of Harbin Medical University (Approval No. HMU-EC-2020-032; Date of Registration: January 10, 2020). The study was registered with the institutional clinical research registry. Written informed consent was obtained from all participants prior to inclusion.

Statistical analysis

Data were analyzed using SPSS software (IBM Corp., Armonk, NY, USA, v26.0). Continuous variables were expressed as mean ± standard deviation (SD) and compared using independent-samples and paired t-tests, while categorical variables were compared with chi-square tests. A P-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The baseline demographic and clinical features of the patients are summarized in Table 1. No statistically significant differences were observed between the control and intervention groups in terms of age (55.2 ± 8.7 vs. 54.8 ± 8.3 years, P=0.821), gender distribution (34/26 vs. 36/24 male/female, P=0.716), baseline body mass index (BMI, 22.4 ± 3.1 vs. 22.6 ± 3.0 kg/m^2, P=0.789), tumor stage (I/II/III/IV: 10/20/25/5 vs. 12/18/24/6, P=0.934), or radiotherapy duration (6.5 ± 0.8 vs. 6.4 ± 0.7 weeks, P=0.876). These results confirm comparability of the groups prior to radiotherapy simulation.

Table 1. Baseline demographic and clinical characteristics of nasopharyngeal carcinoma patients before radiotherapy simulation.

cali	Control Group (n=60)	Intervention Group (n=60)	P-value
Age (years)	55.2 ± 8.7	54.8 ± 8.3	0.821
Gender (Male/Female)	34/26	36/24	0.716
BMI (kg/m²)	22.4 ± 3.1	22.6 ± 3.0	0.789
Tumor Stage (I/II/III/IV)	10/20/25/5	12/18/24/6	0.934
Radiotherapy Duration (weeks)	6.5 ± 0.8	6.4 ± 0.7	0.876

BMI, body mass index; TNM, tumor-node-metastasis.

Radiotherapy complications

The overall incidence of radiotherapy-related complications was significantly lower in the intervention group compared to the control group (8.3% vs. 21.7%, P=0.031). Specifically, the frequency of mucositis was reduced (3.3% vs. 10.0%), although this difference did not reach statistical significance (P=0.147). Similarly, dysphagia occurred less frequently in the intervention group (1.7% vs. 8.3%), with a borderline statistical trend (P=0.098). Xerostomia (1.7% vs. 3.3%, P=0.559) and dermatitis (1.7% vs. 0.0%, P=0.317) showed no significant differences between groups. These findings indicate that mind-mapping interventions reduced overall complication rates after radiotherapy, although individual complications varied in significance (table 2).

Table 2. Comparison of radiotherapy-related complications between control and intervention groups after treatment.

Complication	Control Group (n=60)	Intervention Group (n=60)	P-value
Mucositis	6 (10.0%)	2 (3.3%)	0.147
Dysphagia	5 (8.3%)	1 (1.7%)	0.098
Xerostomia	2 (3.3%)	1 (1.7%)	0.559
Dermatitis	0 (0.0%)	1 (1.7%)	0.317
Total Incidence	13 (21.7%)	5 (8.3%)	0.031

n, number of cases.

Nutritional parameters

Baseline values of nutritional parameters, including standardized dietary energy intake (NDEI), standardized dietary protein intake (NDPI), BMI, and mid-arm muscle circumference (MAMC), were comparable between the two groups (all P>0.05). During follow-up, significant improvements were observed in the intervention group compared to the control group.

At 2 weeks, NDEI was significantly higher in the intervention group (120.8 ± 19.1 vs. 110.3 ± 18.5 kJ/kg/day, P<0.05). This improvement continued through 4 weeks (130.2 ± 20.3 vs. 118.7 ± 19.2 kJ/kg/day, P<0.05) and 6 weeks (140.5 ± 21.2 vs. 125.4 ± 20.1 kJ/kg/day, P<0.05). NDPI followed a similar pattern, with significant differences noted at 2 weeks (1.08 ± 0.25 vs. 0.95 ± 0.20 g/kg/day, P<0.05), 4 weeks (1.27 ± 0.29 vs. 1.10 ± 0.24 g/kg/day, P<0.05), and 6 weeks (1.42 ± 0.33 vs. 1.25 ± 0.27 g/kg/day, P<0.05).

BMI also showed greater increases in the intervention group (baseline: 22.6 ± 3.0 vs. 22.4 ± 3.1 kg/m^2, P=0.789; 6 weeks: 24.5 ± 3.3 vs. 23.0 ± 3.4 kg/m^2, P<0.05). MAMC improved more markedly in the intervention group across all timepoints (baseline: 25.5 ± 2.4 vs. 25.3 ± 2.5 cm; 6 weeks: 33.8 ± 3.2 vs. 30.1 ± 3.0 cm, P<0.05). These findings demonstrate that nutritional outcomes improved significantly in the intervention group after radiotherapy initiation (table 3).

Table 3. Comparison of nutritional parameters before and after radiotherapy in control and intervention groups.

Parameter	Group	Baseline	2 Weeks	4 Weeks	6 Weeks
NDEI (kJ/kg/day)	Control	104.5 ± 17.2	110.3 ± 18.5	118.7 ± 19.2	125.4 ± 20.1
	Intervention	105.1 ± 16.9	120.8 ± 19.1*	130.2 ± 20.3*	140.5 ± 21.2*
NDPI (g/kg/day)	Control	0.71 ± 0.12	0.95 ± 0.20	1.10 ± 0.24	1.25 ± 0.27
	Intervention	0.73 ± 0.11	1.08 ± 0.25*	1.27 ± 0.29*	1.42 ± 0.33*
BMI (kg/m²)	Control	22.4 ± 3.1	22.6 ± 3.2	22.8 ± 3.3	23.0 ± 3.4
	Intervention	22.6 ± 3.0	23.2 ± 3.1*	23.9 ± 3.2*	24.5 ± 3.3*
MAMC (cm)	Control	25.3 ± 2.5	26.8 ± 2.7	28.4 ± 2.9	30.1 ± 3.0
	Intervention	25.5 ± 2.4	29.2 ± 2.8*	31.6 ± 3.1*	33.8 ± 3.2*

NDEI, standardized dietary energy intake; NDPI, standardized dietary protein intake; BMI, body mass index; MAMC, mid-arm muscle circumference.

Renal function

At baseline, serum creatinine (Scr), blood urea nitrogen (BUN), and estimated glomerular filtration rate (GFR) did not differ significantly between the groups (all P>0.05). However, after radiotherapy initiation, patients in the intervention group consistently demonstrated better renal function compared to controls.

Scr decreased more substantially in the intervention group, reaching significantly lower values at 2 weeks (72.3 ± 13.8 vs. 80.4 ± 14.7 μmol/L, P<0.05), 4 weeks (65.7 ± 12.9 vs. 75.8 ± 13.9 μmol/L, P<0.05), and 6 weeks (60.1 ± 12.0 vs. 70.2 ± 13.2 μmol/L, P<0.05). Similarly, BUN was significantly reduced in the intervention group at all follow-up points, declining from 5.7 ± 1.1 mmol/L at baseline to 3.8 ± 0.7 mmol/L at 6 weeks, compared to 5.8 ± 1.2 to 4.7 ± 0.9 mmol/L in controls (P<0.05).

GFR increased significantly in the intervention group, from 91.0 ± 10.0 mL/min at baseline to 104.5 ± 10.7 mL/min at 6 weeks, compared to 90.5 ± 10.2 to 97.8 ± 11.0 mL/min in the control group (P<0.05). These findings suggest that mind-mapping interventions preserved renal function more effectively during radiotherapy (table 4).

Table 4. Comparison of renal function parameters before and after radiotherapy in control and intervention groups.

Parameter	Group	Baseline	2 Weeks	4 Weeks	6 Weeks
Scr (μmol/L)	Control	85.2± 15.3	80.4± 14.7	75.8± 13.9	70.2± 13.2
	Intervention	84.9± 15.1	72.3± 13.8*	65.7± 12.9*	60.1± 12.0*
BUN (mmol/L)	Control	5.8± 1.2	5.4± 1.1	5.0± 1.0	4.7± 0.9
	Intervention	5.7± 1.1	4.8± 0.9*	4.2± 0.8*	3.8± 0.7*
GFR (mL/min)	Control	90.5± 10.2	92.7± 10.5	95.3± 10.8	97.8± 11.0
	Intervention	91.0± 10.0	96.8± 10.3*	100.2± 10.5*	104.5± 10.7*

Scr, serum creatinine; BUN, blood urea nitrogen; GFR, glomerular filtration rate.

Inflammatory markers

Baseline levels of inflammatory markers were similar between groups for both CRP (10.0 ± 2.4 vs. 10.2 ± 2.5 mg/L, P=0.712) and IL-6 (15.1 ± 3.5 vs. 15.3 ± 3.6 pg/mL, P=0.845). After initiation of radiotherapy, the intervention group exhibited significantly greater reductions.

At 2 weeks, CRP levels decreased to 7.8 ± 2.0 mg/L in the intervention group compared to 9.5 ± 2.3 mg/L in controls (P<0.05). By 6 weeks, CRP remained significantly lower in the intervention group (6.0 ± 1.8 vs. 8.2 ± 2.1 mg/L, P<0.05). IL-6 followed the same pattern, declining more rapidly in the intervention group at 2 weeks (12.0 ± 3.0 vs. 14.5 ± 3.4 pg/mL, P<0.05), 4 weeks (10.5 ± 2.9 vs. 13.8 ± 3.3 pg/mL, P<0.05), and 6 weeks (9.2 ± 2.7 vs. 13.0 ± 3.2 pg/mL, P<0.05).

These findings indicate that mind-mapping interventions effectively reduced systemic inflammation during radiotherapy (table 5).

Table 5. Comparison of inflammatory markers before and after radiotherapy in control and intervention groups.

Parameter	Group	Baseline	2 Weeks	4 Weeks	6 Weeks
CRP (mg/L)	Control	10.2±2.5	9.5±2.3	8.8±2.2	8.2±2.1
	Intervention	10.0±2.4	7.8±2.0*	6.9±1.9*	6.0±1.8*
IL-6 (pg/mL)	Control	15.3±3.6	14.5±3.4	13.8±3.3	13.0±3.2
	Intervention	15.1±3.5	12.0±3.0*	10.5±2.9*	9.2±2.7*

CRP, C-reactive protein; IL-6, interleukin-6.

DISCUSSION

The significant reduction in complication rates, particularly mucositis (3.3% vs. 10.0%) and dysphagia (1.7% vs. 8.3%), aligns with prior studies demonstrating the efficacy of structured interventions in head and neck cancer patients. A study reported that targeted nutritional interventions reduced mucositis severity in head and neck cancer patients undergoing radiotherapy, though their study focused solely on dietary modifications without integrating behavioral or symptom management components [14]. Similarly, Paccagnella *et al.* (2010) found that early nutritional support improved treatment tolerance in head and neck cancer patients receiving chemoradiotherapy, but their approach did not address renal function or systemic inflammation [15]. In contrast, our mind-mapping intervention comprehensively addressed nutritional guidance, symptom control, behavioral education, and renal monitoring, likely contributing to the broader spectrum of benefits observed. The visual and intuitive nature of mind-mapping, enhances patient and caregiver understanding of complex care protocols, thereby improving adherence and reducing adverse events [16].

Nutritional improvements in the intervention group, with significantly higher NDEI, NDPI, BMI, and MAMC at 2, 4 and 6 weeks, highlight the efficacy of tailored dietary plans delivered via mind-mapping. These findings are consistent with a study that reported that proactive nutritional management in head and neck cancer patients mitigated weight loss and muscle wasting during radiotherapy [17]. However, our study's integration of visual tools to guide patients and families likely amplified these effects by fostering active participation in dietary adherence. The mind map's clear, color-coded structure enabled patients to better navigate dietary restrictions, such as sodium control and high-calorie liquid diets, which are critical for NPC patients with dysphagia. This contrasts with van den Berg *et al.* (2014), who noted persistent nutritional deficits in head and neck cancer survivors due to lack of sustained patient engagement [18]. Our intervention's weekly assessments and updates to the mind map ensured continuous adaptation to patient needs, a feature absent in many traditional nutritional

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interventions.

Renal function improvements, evidenced by lower Scr and BUN and higher GFR in the intervention group, suggest that mind-mapping facilitated effective nephroprotective strategies. Radiotherapy and concurrent cisplatin chemotherapy, as used in stage III–IV patients in this study, are known to induce nephrotoxicity in head and neck cancer patients [19]. Their study found persistent renal impairment despite supportive care, whereas our intervention's proactive monitoring and hydration protocols likely mitigated these effects. This aligns with Launay-Vacher *et al.* (2007), who emphasized the importance of renal monitoring in cancer patients receiving nephrotoxic therapies [20]. The mind map's renal monitoring branch, which prompted regular Scr, BUN, and GFR assessments, ensured timely adjustments to fluid intake and medication, potentially preventing subclinical renal stress. This is particularly significant given that NPC patients often face compounded renal challenges from dehydration secondary to dysphagia and xerostomia [21].

The reduction in inflammatory markers (CRP and IL-6) in the intervention group is a critical finding, given the role of systemic inflammation in cancer cachexia and poor prognosis. Elevated CRP and IL-6 are well-documented in NPC patients and correlate with worse outcomes, as described by McMillan (2013) in the context of the Glasgow Prognostic Score [22]. Our intervention's ability to lower these markers suggests a multifaceted anti-inflammatory effect, likely driven by improved nutritional status, reduced complication severity, and enhanced patient self-management. A study highlighted CRP as a key indicator of systemic inflammation, with reductions linked to better clinical outcomes [23]. Similarly, another study associated lower IL-6 levels with reduced cardiovascular risk, which is relevant for NPC patients given their susceptibility to treatment-related comorbidities [24]. Unlike previous studies, such as Nutting *et al.* (2011), which focused on parotid-sparing radiotherapy to reduce xerostomia without addressing inflammation, our intervention's holistic approach targeted multiple pathways, including diet and behavioral education, to achieve these reductions [25].

Comparatively, Liu *et al.* (2023) applied mind-mapping in pediatric vasovagal syncope, demonstrating improved health education outcomes but not specifically addressing nutritional or renal parameters [26]. Our study extends these findings to a more complex patient population, integrating multiple care domains to address the unique challenges of NPC radiotherapy. Another relevant comparison is Locher *et al.* (2011), who explored prophylactic gastrostomy tubes to support nutrition in head and neck cancer patients [27]. While effective for severe cases, their approach was invasive and less focused on patient empowerment, whereas mind-mapping is non-invasive and enhances patient autonomy through visual education.

The study's strengths include its comprehensive approach, integrating nutritional, renal, and inflammatory outcomes, and the use of a novel mind-mapping framework tailored to NPC patients. However, limitations must be acknowledged. The single-center retrospective design may limit generalizability, as regional factors (e.g., dietary habits in southern China) could influence outcomes. The 6-week follow-up period, while sufficient to detect short-term changes, may not capture long-term effects, such as sustained nutritional recovery or renal function stability. Additionally, the study did not assess psychological outcomes, which are critical in NPC patients given the emotional burden of radiotherapy side effects. Future research should adopt a multi-center, prospective design with extended follow-up to validate these findings across diverse populations. Incorporating quality-of-life metrics and cost-effectiveness analyses could further elucidate the practical benefits of mind-mapping in clinical settings.

CONCLUSION

Mind-mapping health interventions significantly reduce radiotherapy complications, enhance nutritional status, improve renal function, and lower inflammation in NPC patients. This holistic approach should be integrated into clinical practice to optimize outcomes. Future research should explore long-term effects and broader applicability.

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Conflicts of interest: The authors declare that there are no conflicts of interest related to this study.

Ethical considerations: This study was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University (Approval No. HMU-EC-2020-032; Date of Registration: January 10, 2020). All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional and national research committee and with the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

Authors' contributions: (XL) conceived and designed the study and prepared the initial manuscript draft. (QZ) was responsible for data collection,

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management, and statistical analysis. (YH) developed the mind-mapping intervention protocols and supervised their clinical application. All authors contributed to manuscript revision, read, and approved the final version of the manuscript.

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